ARCHIVES OF PATHOLOGY

VOLUME 27 JUNE 1939 NUMBER 6

ACCESSORY ADRENAL CORTICAL TISSUE

ARTHUR A. NELSON, M.D., PH.D.

WASHINGTON, D. C.

An accumulation of accessory adrenal cortical tissues from 19 persons, together with the unorganized state of the literature on this subject, has prompted the writing of this paper. Ten of these 19 specimens of accessory cortical tissue were found in the immediate vicinity of testes; 6 of these 10 specimens were obtained from adults, making this the largest group of the kind reported; 1 specimen was of tumor proportions and apparently the largest mass of this type yet observed in this situation.

Accessory adrenal tissue in the near vicinity of the adrenal was first described by Morgagni,[1] in 1740. Accessory adrenal cortical tissue at a distance from the adrenal was first described by Marchand,[2] in 1883. Over a period of seven years Marchand found yellow nodules, from 1 to 3 mm. in diameter, in the free edge of the broad ligament near the ovary in 5 newborn and older infants, and in a fetus of 5 months he found a similar nodule on each side between the lower pole of the kidney and the broad ligament; microscopically these nodules had the structure of adrenal cortex. Reports by eight other authors of the finding of accessory adrenal tissue in the broad ligament, in adults as well as in newborn infants, published up to 1900, were listed by Aichel,[3] who described several such observations of his own in fetuses and newborn infants.

Chiari,[4] one year after Marchand, was the first to describe accessory cortical adrenal tissue at a distance from the adrenal in adults. In men of 23 and 34 years and in a woman of 30 years he found accessory nodules below the lower pole of the right kidney, in the vicinity of or lying on the spermatic and ovarian veins; in a woman of 48 years there was a nodule on the right side anterior to the ovarian veins at

From the National Institute of Health.

1. Morgagni, G., cited by Wiesel, J.: Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. (Abt. 3) **108**:257, 1899.
2. Marchand, F.: Virchows Arch. f. path. Anat. **92**:11, 1883.
3. Aichel, O.: Arch. f. mikr. Anat. **56**:1, 1900.
4. Chiari, H.: Ztschr. f. Heilk. **5**:449, 1884.

the level of the linea terminalis of the pelvis, and on the left side, two nodules in the broad ligament. All of these nodules varied from submaxillary to pea size. In the same year d'Ajutolo [5] reported a cherry-sized nodule on the spermatic cord of a newborn infant, just above the internal ring.

The first to describe accessory adrenal cortical tissue in the near vicinity of the testis was Dagonet,[6] in 1885; in a 21 day old infant he found two accessories, each 3 mm. in diameter, one on the internal spermatic plexus (side not stated) and one between the right testis and the epididymis. Other reported cases of accessory adrenal tissue near or in the testis or ovary will be considered later.

The cases of accessory adrenal cortical tissue reported before 1900 were reviewed by Wiesel [7] and Aichel.[3] Weller [8] reviewed the 13 reported cases (to 1925) of true renal or hepatic adrenal heterotopia (no adrenal except the inclusion present on that side) and added 4 cases of his own.

Jaffe in his review [9] and Goldzieher [10] in his book on the adrenals mentioned accessory tissue only briefly.

SYSTEMATIC STUDIES OF OCCURRENCE OF ADRENAL ACCESSORIES

No systematic study of human material with respect to the occurrence of accessory adrenal cortical tissue in all locations where it might be reasonably expected to occur has ever been published. There are a few reports of studies of one particular region in more or less large numbers of cases. Schmorl [11] reported finding small masses (three in one case) of adrenal cortical tissue just under the capsule of the right lobe of the liver, close to the adrenal, in 4 of 510 persons examined post mortem within a period of seven months; 2 of these were men of 24 and 56 years and 2 were women of 36 and 37 years; most of the masses were of pinhead size, while the largest was lentil size. Schmorl also found a pea-sized nodule just outside the external inguinal ring on the right spermatic cord of a man 30 years of age.

Concerning the occurrence of accessory tissue in the kidney, Lubarsch [12] briefly stated that he had found adrenal cortical tissue in

5. d'Ajutolo, G.: Arch. per le sc. med. **8**:283, 1884.

6. Dagonet, J.: Ztschr. f. Heilk. **6**:1, 1885.

7. Wiesel, J.: Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. (Abt. 3) **108**:257, 1899.

8. Weller, C. V.: Am. J. M. Sc. **169**:696, 1925.

9. Jaffe, H. L.: Arch. Path. **3**:414, 1927.

10. Goldzieher, M.: The Adrenals, New York, The Macmillan Company, 1929.

11. Schmorl, G.: Beitr. z. path. Anat. u. z. allg. Path. **9**:523, 1891.

12. Lubarsch, O.: Virchows Arch. f. path. Anat. **135**:149, 1894.

the kidney in 8 of 300 bodies and "much more frequently" along the adrenal and internal spermatic veins. Glynn [13] found no accessory tissue in 1,500 kidneys. Brites [14] examined the kidneys of 376 bodies and found accessory adrenal cortical tissue in 10; later he found none in 1,100 human kidneys, 1,060 sheep kidneys, 34 goat kidneys and 58 beef kidneys. My own 5 examples were found among 630 persons examined post mortem. McLennan,[15] examining the hernial sacs removed at operation from 700 children (660 of whom were boys), found nodules of adrenal cortical tissue embedded in the walls of 6 of the sacs. These nodules were near, but not attached to, the spermatic cord. He had not seen any such nodules in adults.

The only reported systematic study of the testes for the presence of accessory adrenal cortical tissue is that of Wiesel,[7] who examined 15 pairs of testes and epididymides from newborn infants and an equal number from children over 1 year of age and adults. In 13 of the newborn infants bits of accessory tissue were found on one side (9 on the right, 4 on the left) and in 5 on both sides; thus, in 23 (76.5 per cent) of the 30 gonads altogether. The most common location was in the connective tissue around the tail of the epididymis. No fully developed accessory tissue was found in the testes of the children and adults, although in the younger persons especially, Wiesel stated, he could find cell masses and strands which had somewhat the appearance of adrenal cortex and which could be thought of as being in a stage of regression.

ACCESSORY ADRENAL CORTICAL TISSUE IN ANIMALS

The occurrence of accessory adrenal cortical tissue in animals has been known since at least 1887, when Canalis [16] found among 40 rabbits 2 adrenal accessories of rice grain size, each on the right side, near the mouth of the renal vein; these were composed of cortical tissue only. Wiesel [7] found adrenal accessories in about 50 per cent of rats, and more in sexually active than in very young or very old rats. Jaffe [9] found gross accessories in about 8 per cent of normal rats and in from 20 to 25 per cent after double adrenalectomy; these accessories were always situated near the main glands, and Jaffe could find none in the region of the testis, vas and epididymis. Microscopically he could find accessories on serial section of the retroperitoneal tissues in

13. Glynn, E. E.: Quart. J. Med. **5**:157, 1912; J. Obst. & Gynaec. Brit. Emp. **28**:23, 1921.
14. Brites, G.: Folia anat. univ. conimb. **10**:1, 1935.
15. McLennan, A.: Surg., Gynec. & Obst. **29**:387, 1919.
16. Canalis, P.: Internat. Monatschr. f. Anat. u. Physiol. **4**:312, 1887.

70 per cent of rats before sexual maturity. Marine and Baumann [17] reported gross accessories in 70 per cent of rabbits after adrenalectomy.

The constant occurrence of adrenal cortical tissue within the genital tract of both the male and the female rabbit has been recently established by Lacassagne and Nyka.[18] In every one of 10 adult male rabbits a nodule of adrenal cortical tissue was found, usually in the adipose tissue around the posteroinferior portion of the head of the epididymis at the level of the junction of the rete testis and efferent ducts; it was on the right side in 5, on the left in 4 and bilateral in 1. In 10 female rabbits serial sections of the adnexae showed a similar structure in all, 8 times on the right side, once on the left, and once bilaterally.

FREQUENCY OF OCCURRENCE OF ACCESSORY TISSUE

A statement which has been frequently quoted, often at second hand and often in various erroneous forms, and which deserves some explanation at this time, is to the effect that Schmorl found accessory adrenals in 92 per cent of all bodies. Such a statement without further qualification might well give rise to the idea that these were accessory adrenals at some distance from the main glands and that one or more such bodies could be found in nearly every cadaver. This statement or references to statements based on it may be found in such current sources of information about the adrenals as Goldzieher [19] and Ewing.[19] In these and in various papers on accessory adrenals eventual reference is made to a paper by Schmorl appearing in volume 9 of the *Beiträge zur pathologischen Anatomie und zur allgemeinen Pathologie* for the year 1891. The fact is that in this particular paper [11] Schmorl made no such statement. However, in the same number of that journal, in a paper concerning tumors thought to arise from adrenal rests, by Beneke,[20] the statement is made that *die "Versprengung" von Nebennierenkeimen findet sich, wie ich von Herrn Collegen Dr. Schmorl auf Grund einer von ihm aufgestellten Statistik erfahre, bei 92% aller Leichen, meist in der nächsten, aber auch in der weiteren Umgebung der Nebennieren.* . . . (The "scattering" of adrenal rests, as I learned from Dr. Schmorl, on the basis of statistics compiled by him, is this—that adrenal rests are found in 92 per cent of all bodies, usually in the immediate vicinity, but also in the more distant vicinity, of the adrenals.) During the next few years this statement

17. Marine, D., and Baumann, E. J.: J. Metab. Research **1**:777, 1922.

18. Lacassagne, A., and Nyka, W.: Compt. rend. Soc. de biol. **118**:1406, 1935; **121**:95, 1936.

19. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

20. Beneke, R.: Beitr. z. path. Anat. u. z. allg. Path. **9**:440, 1891.

was misquoted on so many occasions that Rossa [21] asked Schmorl himself about it and discussed it and the misquotations of the latter's paper. According to Rossa, Schmorl found accessory adrenal tissue in 92 per cent of "a large number" of bodies, nearly all of adults; included were those accessories in the immediate vicinity of the adrenal, in the strands of the solar plexus and along the adrenal and spermatic veins, but not those in the renal cortex or the under surface of the liver; in all doubtful cases microscopic examination was done. The important fact is that no figure for each separate location was given; in all probability, the great majority of the 92 per cent were accounted for by those in the immediate vicinity of the adrenal, and accessory adrenal cortical nodules at any distance from the adrenal will undoubtedly be found to occur in far less than 92 per cent of bodies of all ages.

ACCESSORY TISSUE WITHIN THE TESTIS OR OVARY

In all the reported cases of accessory adrenal cortical tissue in the vicinity of the testis and epididymis, the tissue has been situated in the mediastinum testis, the tunics of the testis, the connective tissue between the testis and the epididymis, near the epididymis or within the epididymis (a few cases). No one has yet reported a case of adrenal tissue situated deep within the testis, and only R. Meyer [22] has reported an instance in which the accessory tissue appears to be underneath the tunica albuginea; this was a small nodule in a fetus. Two of Wiesel's [7] accessory nodules in newborn infants were within the epididymis, among the tubules; Kirkbride [23] illustrated an accessory nodule among the ducts of the epididymis in a newborn infant; Marsella [24] did the same for a man 37 years of age.

In the ovary, adrenal cortical tissue was first reported by Lodi,[25] in 1902. He found nodules from pea to hazelnut size in the ovaries of a woman who had been pregnant fourteen times. Some of the nodules had masses of fibrin in their centers, making it probable that these were masses of lutein cells. Marchetti [26] found, among 1,200 autopsies, what he thought were 2 small masses of adrenal cortical cells near a cyst in an ovary from an adult woman. Varaldo [27] in the same year reported rests, 5 to 7 mm. in diameter, in the ovaries of 3 women from 30 to 41 years of age (1 in each instance). These were

21. Rossa, E.: Arch. f. Gynäk. **56**:296, 1898.
22. Meyer, R.: Ztschr. f. Geburtsh. u. Gynäk. **71**:221, 1912.
23. Kirkbride, M. B.: Arch. f. Entwcklngsmechn. d. Organ. **32**:717, 1911.
24. Marsella, A.: Arch. ital. di urol. **11**:281, 1934.
25. Lodi, M.: Arch. ital. de biol. **37**:486, 1902.
26. Marchetti, G.: Virchows Arch. f. path. Anat. **177**:227, 1904.
27. Varaldo, F.: Arch. di ostet. e ginec. **11**:725, 1904.

also near cysts. Jessup [28] found a circular group of cells in the cortex of an ovary from a 16 day old girl. The outer cells resembled the zona glomerulosa of the adrenal cortex; the inner, the zona fasciculata. There is no illustration and no mention of a fat stain. Berger,[29] in reporting a case of pheochrome tissue in the ovarian hilus of a newborn infant, stated briefly that he had seen adrenal cortical tissue three times in the testis and thirteen times in the ovary; details of the exact locations he did not give.

ADRENAL TISSUE IN HEAD REGION

A unique case is that reported by A. W. Meyer,[30] who found an encapsulated nodule, 0.8 by 1.5 cm., attached to the spinal portion of the eleventh cranial nerve. Microscopically it had the appearance of adrenal zona glomerulosa and zona fasciculata with medulla-like cells in the center. The capsule contained masses of chromaffin cells and a bundle of striated muscle.

TUMORS ARISING FROM ACCESSORY ADRENALS

Following the idea of Grawitz [31] in 1883 that renal hypernephroma arises from accessory adrenal tissue, investigators similarly described tumors in other locations, especially tumor in the ovary. The most thorough articles on this subject were contributed by Glynn.[13] He accepted only 1 case, that observed by Bovin,[32] as an instance of a tumor arising from an adrenal rest. In this case a tumor in the broad ligament of a woman of 28 years caused amenorrhea and the development of a beard. Menstruation returned after removal of tumor; the beard persisted. Kolodny [33] reported the case of a 37 year old woman whose amenorrhea and hirsutism were relieved by removal of a 1,250 Gm. retroperitoneal epigastric tumor, which was invading the stomach; histologically the tumor was composed of wide anastomosing strands of large clear cells containing abundant lipoid droplets and resembling the zona fasciculata of the adrenal. However, the patient died seven months after operation, with pulmonary metastases; an autopsy was not mentioned. Saphir and Parker [34] reported another case of adrenal virilism in a girl of 15 years; here it was thought that a small nest of cells in the right ovary, resembling adrenal cortex, might have been responsible.

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28. Jessup, D. S. D.: Proc. New York Path. Soc. **13**:67, 1913.
29. Berger, L.: Arch. d'anat. micr. **32**:315, 1936.
30. Meyer, A. W.: Anat. Rec. **12**:43, 1917.
31. Grawitz, P.: Virchows Arch. f. path. Anat. **93**:39, 1883.
32. Bovin, E.: Nord. med. Ark. (sect. 1), 1908, vol. 41, no. 15.
33. Kolodny, A.: J. A. M. A. **102**:925, 1934.
34. Saphir, W., and Parker, M. L.: J. A. M. A. **107**:1286, 1936.

PERSONAL OBSERVATIONS

I wish to report 10 examples of accessory adrenal cortical tissue (1 of tumor proportions) in the near vicinity of the testis, 5 of accessory tissue under the capsule of the kidney, 2 of such tissue on the spermatic

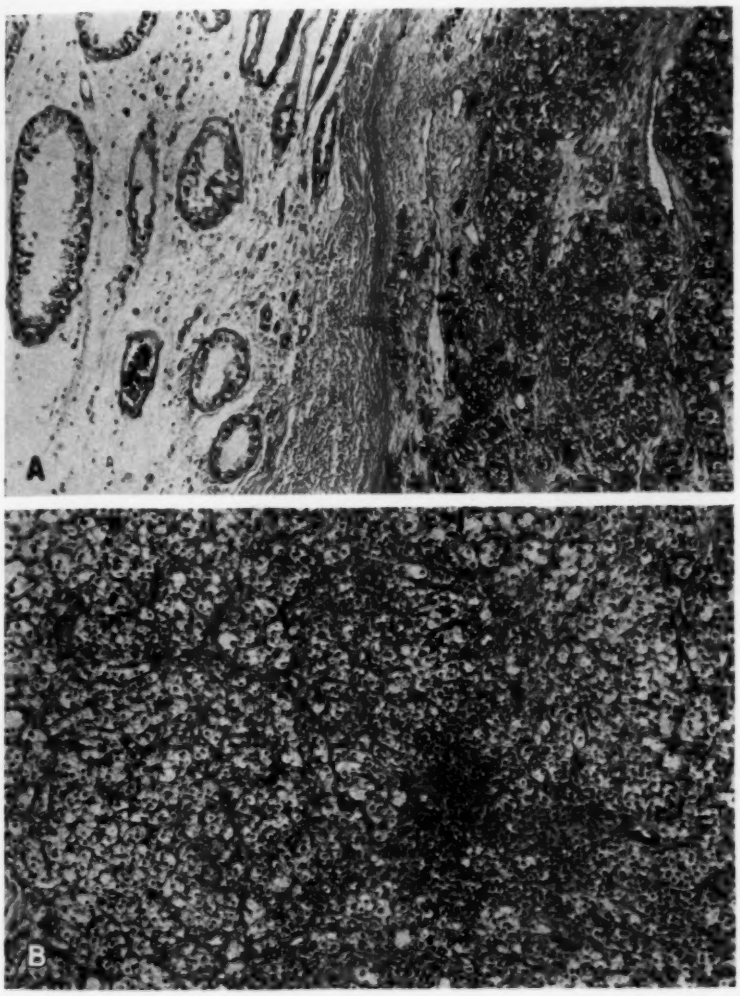

Fig. 1 (case 1).—*A*, section showing the closeness of the adrenal cortical nodule to the testicular tubules; × 75. *B*, interior of tumor; × 75.

cord and 1 of such tissue in the broad ligament. The first, an accessory adrenal cortical nodule, 1.7 cm. in diameter, enclosed in the tunica albuginea of the testis, is presented through the courtesy of Dr. G. L.

Berdez, pathologist of St. Mary's Hospital, Duluth, Minn. This nodule appears to be the largest of its type yet observed in this situation.

CASE 1.—A Jew, a man 35 years of age, noted a small tumor of the right testis three years prior to examination; the nodule did not grow, but he became worried about it; his father had died at the age of 36 from a malignant growth of the testis. Physical examination showed a firm smooth mass, about 1 cm. in diameter, at the lower pole of the right testis; this mass seemed to be a part of the testis, but its outline was easily determined; it was not painful to palpation. At operation it was found to be encapsulated and was easily shelled out. Gross examination showed an almost spherical tumor, 1.7 cm. in diameter, covered by a thin fibrous capsule. On cut section the tumor tissue was of moderately firm consistency and bright yellow. Microscopic examination showed that the tissue was formed by cords of large and medium-sized polyhedral cells with foamy

TABLE 1.—*Accessory Adrenal Cortical Nodules Near Testes*

Case	Age, Yr.	Cause of Death	Side	Size, Mm.	Comment	Atrophy of Testis
2	44	Carcinoma of prostate..	R	3	.....	Moderate
3	42	(Operative specimen)....	R	2	.....	Very marked
4	Newborn	(Premature, 1,550 Gm.)..	?	1 each (2)	.....	None
5	Newborn	(Stillborn, 3,270 Gm.)....	?	1.5	.....	None
6	63	Carcinoma of bladder...	Bilateral	R—1 × 2 L—1.5 × 3	Moderate regression	Marked
7	5	Lymphatic leukemia.....	?	1	Slight regression	None
8	71	Osteogenic sarcoma.....	L	0.5 × 1	Marked regression	Moderate
9	2½	Hydronephrosis.....	?	0.5	Moderate regression	None
10	61	Pernicious anemia.....	L	1 × 2	Marked regression	Marked
11	47	Carcinoma of mouth....	?	1.5 × 2	Moderate regression	Moderate

reticulated cytoplasm and nuclei and nucleoli of moderate size. There was a very marked resemblance to adrenal cortex. Groups of cords were separated by thin and thick fibrous septums. Only few mitoses were seen. Sections stained with scarlet red showed the cells heavily loaded with fat; the sections grossly were of a deep red color. The pathologic diagnosis was "cortical adrenal adenoma of the testis." Figure 1 *A* shows how closely the tumor tissue approached the testicular tubules, and figure 1 *B* gives a better view of the tumor tissue.

The remaining examples are from autopsy and surgical material received at the National Institute of Health and from material obtained at autopsies made by myself at the University of Minnesota. Sections of the testes and epididymides were made without regard to the possible presence of adrenal rests, and for this reason it is difficult to give the exact frequency of these bits of accessory tissue; this would require serial sectioning. None of these nodules were noted grossly. The 5

cases of accessory tissue under the capsule of the kidney and that of a nodule in the broad ligament were encountered among 630 autopsies made by me; here, of course, the surface of each kidney was inspected according to routine and a definite figure for the incidence of accessory

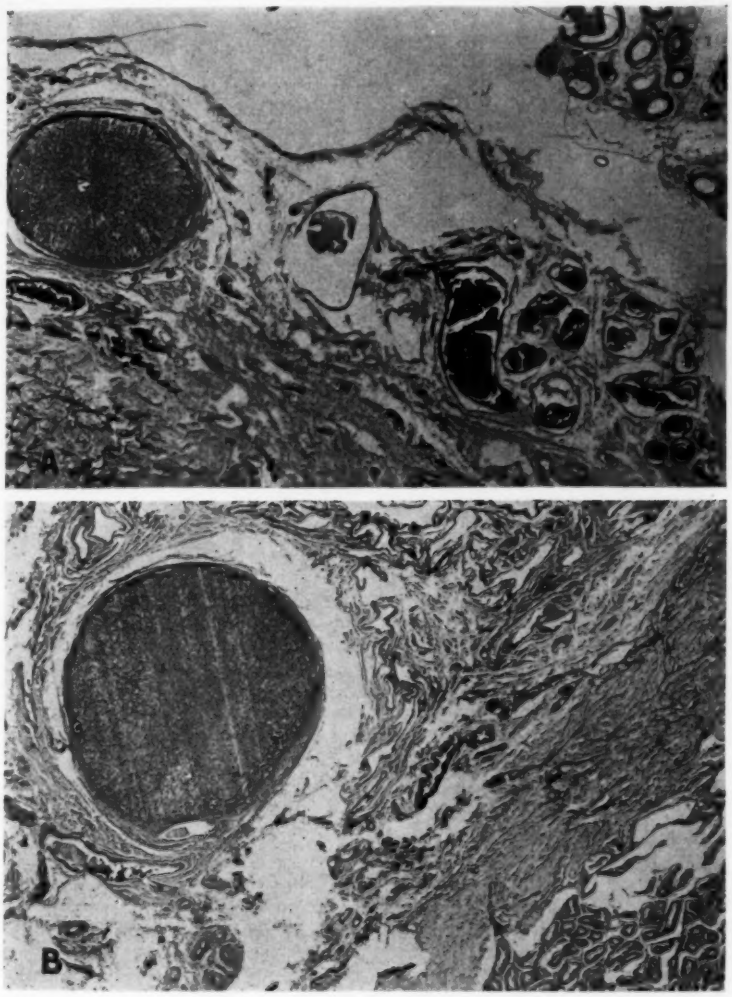

Fig. 2.—*A*, adrenal cortical nodule adjacent to testis (case 3); × 9. *B*, adrenal cortical nodule adjacent to testis (case 2); × 8.

nodules can be given; as previously mentioned, it agrees fairly well with the figures reported in the literature.

In all 10 cases listed in table 1 (case 1 is not included) the accessory adrenal cortical nodule was found in one general location, namely,

either within or just outside the tunica albuginea and either behind or just above or below the rete testis (fig. 2*A* and *B*). In 4 of the 10 cases the nodule showed microscopically the typical structure of

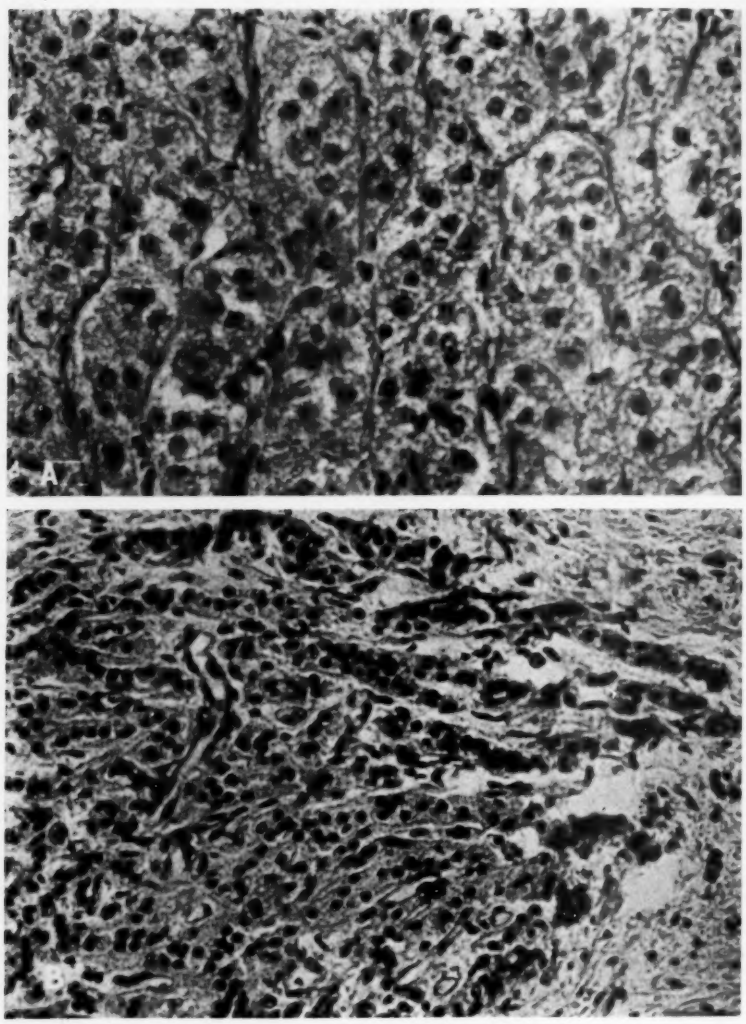

Fig. 3.—*A*, high power view of accessory nodule, showing appearance identical with that of zona fasciculata of adrenal cortex (case 2); × 220. *B*, adrenal cortical nodule undergoing regression (case 9); × 180.

adrenal cortex (fig. 3 *A*); in the other 6 instances there were fibrotic and atrophic changes varying from slight to marked in degree; such changes are in all probability retrogressive, and an example of the

moderate type is shown in figure 3*B*. (This was the smallest accessory nodule observed; more marked retrogressive changes were seen in larger nodules.) The cells lose more or less of their foamy appearance and of the reticulation of their cytoplasm, are smaller and appear much like the cells usually seen immediately under the capsule of the normal adrenal. They still maintain their arrangement in cords, which serves to distinguish them from the masses of interstitial cells often found in the tunica albuginea [35]; in the latter the cells are much less regular in shape and arrangement, and the masses are usually closely associated with nerve fiber bundles and are seldom as large as the masses of adrenal cortical cells.

TABLE 2.—*Accessory Adrenal Cortical Nodules Under Renal Capsules*

Case	Age, Yr.	Sex	Cause of Death	Comment
12	54	F	Hypertension	Each of these nodules was immediately under the capsule, on the superior pole of the kidney; they were from 1 by 2 to 1.5 by 3 mm. in size. In case 15 two nodules were present in one kidney
13	28	M	Medulloblastoma	
14	83	F	Carcinoma of breast	
15	20	M	Cirrhosis of liver	
16	57	M	Cerebral trauma	

TABLE 3.—*Accessory Adrenal Cortical Nodules on Spermatic Cords*

Case	Age, Yr.	Side	Size, Mm.	Comment	Atrophy of Testis
17	50	R	2	Noted on cord during herniotomy; verified microscopically	?
18	22	L	1 × 1.5	Noted on microscopic examination of tissues from herniotomy	Marked

In addition to the examples listed in the tables I have found at autopsy a 3 mm. yellow nodule of adrenal cortical tissue near the free edge of the left broad ligament in a 62 year old woman who died of bronchial asthma; the nature of the tissue was verified microscopically, as it was in the other 18 tabulated cases.

SUMMARY

There are here reported 19 cases of accessory adrenal cortical tissue; in 10 of these the accessory tissue was found between the testis and the epididymis; in 1 it was at the lower pole of the testis and was of tumor proportions; in 5 it was under the renal capsule; in 2 it was on the spermatic cord, and in 1, in the broad ligament. Fifteen of these 19 persons were adults. A review of the literature is also given.

35. Nelson, A. A.: Am. J. Path. **14**:831, 1938.

ACUTE POSTOPERATIVE ENTEROCOLITIS

A STUDY ON THE PATHOLOGIC NATURE OF SHOCK

ABRAHAM PENNER, M.D.
AND
ALICE IDA BERNHEIM, M.D.
NEW YORK

The chance observation of the sloughing of intestinal mucous membrane following radical mastectomy in a patient with severe diabetes led us to inquire into the factors and mechanisms responsible for this phenomenon. With this in view we reviewed the postmortem records of the Mount Sinai Hospital for similar cases of acute diphtheritic enteritis and, in addition, searched the literature for similar observations. The serious nature of this complication, as well as the importance of the mechanism involved in its production, leads us to report our findings.

HISTORICAL REVIEW

The search of the literature revealed but few reports made in sufficient detail to identify clearly the nature of the process dealt with. The earliest report of a case which we were able to find is that of Finney.[1] This surgeon reported a case of benign pyloric obstruction for which he performed pylorectomy and gastroenterostomy. The patient apparently was well for the first ten postoperative days. Then bloody diarrhea developed, which led to a fatal outcome after five days. The postmortem examination, made by Dr. Simon Flexner, showed that there was no evidence of peritonitis but that the bloody diarrhea was due to diphtheritic enteritis involving the terminal ileum and colon down to and including the rectum, but with diminishing intensity distally. The report contains no microscopic description of the lesion.

Terrier and Hartman,[2] in their monograph on gastric surgery, published in 1899, reported the occurrence of diarrhea in 7 of the 35 cases reported in detail in their text. This diarrhea occurred after gastroenterostomy, pylorectomy or gastrectomy. However, the clinical and pathologic data are so scant that it is impossible to evaluate the cases

From the Laboratories of the Mount Sinai Hospital.

1. Finney, J. M. T.: Bull. Johns Hopkins Hosp. **4**:53, 1893.

2. Terrier, F., and Hartman, H.: Chirurgie de l'estomac, Paris, G. Steinheil, 1899.

properly. Three years later Riedel [3] published a report entitled "Ueber Darmdiphtherie nach schweren Operationem bei sehr geschwächten Kranken." He described 5 cases in which an anatomic diphtheritic lesion of the intestine occurred postoperatively. He recognized the anatomic resemblance of the intestinal lesions to those produced by mercury poisoning and was particularly interested in pointing out that the suture material used in the operations had been thoroughly rinsed free from any significant amount of this substance. His first case occurred in 1899. The lesion involved the colon, apparently mainly in the region of the cecum. The latter was dark red and edematous and showed focal areas covered with a gray to grayish green membrane. These changes occurred after hysterectomy for fibroids in a very anemic, cachectic woman of 47 years, who "went into collapse" twenty-four hours after the operation and died four days later. His second case was that of a 52 year old woman on whom he had performed almost total gastrectomy for an enormous growth extending almost to the cardia. Diarrhea developed three days after the operation, and death occurred twenty-four hours later. Autopsy showed the typical lesion involving the lower part of the jejunum, the cecum and the transverse colon, with apparently normal intestine intervening. There was no peritonitis in either of these cases, and Riedel felt that they were not cases of infectious dysentery. His third case was one in which the diphtheritic lesion occurred after a Billroth 1 operation for pyloric stenosis resulting from drinking sulfuric acid with suicidal intent. This patient did not have postoperative diarrhea but died in "collapse" three days after the operation. Autopsy showed a diphtheritic lesion restricted to the ileum. There was no evidence of peritonitis. In his last 2 cases, although the changes presented post mortem were typical, the findings were complicated by the fact that the affected loops of intestine had been manipulated extensively in the operative procedures. Riedel is particularly emphatic in his assertion that preoperative catharsis was not involved in the pathogenesis of the lesion. He felt that the protracted operation, loss of blood and anesthesia, plus the preoperative "weakness" and anemia, united to make the intestine unable to resist its own contents. "This diphtheria of the intestine is nothing more than a superficial necrosis of a poorly nourished mucosa." This analysis represents the first attempt to correlate the preoperative condition and the operative trauma with the occurrence of the diphtheritic intestinal lesion. Four years later Anschütz,[4] in discussing intestinal disturbances following gastric operations, presented 4 cases of the same type. In these

3. Riedel: Deutsche Ztschr. f. Chir. **67**:402, 1902.

4. Anschütz, W.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **15**:305, 1905.

instances the lesion occurred following gastroenterostomy for a benign lesion or after multiple operations. In 2 of the 4 cases postoperative diarrhea never developed. In addition, Anschütz noted 3 cases in which the typical postoperative diarrhea was present but in which the patient survived, so that anatomic confirmation of the lesion was not obtained. In still another case the diarrhea terminated fatally but autopsy was not done. Anschütz has described the lesion as necrotizing, ulcerative ileitis, colitis and proctitis which diminished in intensity distally. He attributed it to the occurrence of putrefaction in the stomach and intestines of a "cachectic" patient.

The occurrence of diphtheritic enteritis was briefly mentioned by Wertheim,[5] who observed it three times in a series of 500 consecutive cases of radical exenteration of the pelvis for carcinoma of the cervix. The lesion involved the rectum and colon and was invariably associated with a fatal outcome. Rössle[6] also noted 2 instances in which necrotizing diphtheroid colitis followed a pelvic operation. In one the radical Wertheim operation was performed; in the other, lysis of old pelvic adhesions led to purulent peritonitis, which terminated fatally. He emphasized the role played by medicated enemas in causing local trauma. A similar lesion involving the small intestine and cecum was reported by de Rouville and Roger[7] in a patient subjected to hysterectomy. In this instance diarrhea appeared on the eighteenth postoperative day and led to a fatal issue four days later. In this case several of the ulcerations extended deeply enough to perforate.

Finsterer[8] observed acute catarrhal enteritis and colitis following gastric resection in which the entire lesser curvature was removed and only a small portion of the greater curvature remained. Diarrhea developed on the sixth day, and the patient succumbed on the tenth postoperative day.

The first really intensive study of this postoperative complication was made by Bierende.[9] He made a careful investigation of 7 cases. In 5 of these acute peritonitis was present at the time of operation or supervened shortly thereafter. His patients were aged from 50 to 63 years. The operative procedures included: (1) appendectomy for acute appendicitis complicated by purulent paranephritis with perforation into the pleura and empyema; (2) suturing of a perforated duodenal ulcer, which was then side-tracked by gastroenterostomy; (3) Wertheim's procedure for carcinoma of the cervix; (4) gastric

5. Wertheim, E.: Die erweiterte abdominale Operation bei Carcinom colli uteri (auf Grund von 500 Fällen) Berlin, Urban & Schwarzenberg, 1911.

6. Rössle, R.: Monatschr. f. Geburtsh. u. Gynäk. **35**:243, 1912.

7. de Rouville, G., and Roger, H.: Arch. d. mal. de l'app. digestif **7**:24, 1913.

8. Finsterer, H.: Deutsche Ztschr. f. Chir. **128**:514, 1914.

9. Bierende, F.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **32**:85, 1920.

resection for ulcer; (5) gastroenterostomy for ulcer; (6) Witzel's gastrostomy for carcinoma of the esophagus, and (7) resection of a large ovarian cyst. None of the patients had postoperative diarrhea. None survived for more than six days and 4 died within three days after the operation. In 5 of the 7 cases the diphtheritic lesion was restricted to the rectum; in the other 2 cases the colon was involved, diffusely in one, while in the other the lesion was segmentally restricted to the transverse colon. The most significant feature of this study lies in the detailed histologic observations and their correlation with the preoperative and postoperative status of the patient. Bierende's anatomic observations were essentially the same as ours; his analysis of these observations led him to consider the tissue changes as due to vasoparalysis, which led to local circulatory disturbances. He believed that the latter, plus retention of feces, resulted in the terminal lesion.

Goldschmidt and Mülleder [10] noted the occurrence of uncontrollable diarrhea in 30 patients in a series of 500 gastric operations of various types. They pointed out that the clinical symptoms were identical with those of dysentery but that culture of the stools did not yield pathogenic organisms. They presented detailed records of 3 cases and noted that in 7 others the patients recovered after presenting similar clinical features.

Their first case involved a 61 year old man with a pyloric obstruction of ten years' duration. This had finally become complete and had led to advanced cachexia and marasmus. Because of this, posterior gastroenterostomy was done. Six days later the abdominal wound was healed. On the eleventh day bloody diarrhea developed. Nine days later a gastrointestinal roentgenogram showed stenosis in the upper part of the jejunum. This was not found on laparotomy, which revealed a large amount of free fluid in the abdomen. The patient died two days later. Culture of the stool revealed no pathogenic organisms. Postmortem examination revealed acute necrotizing colitis and ileitis.

The second case concerned a 55 year old man on whom subtotal gastrectomy was done for scirrhous carcinoma of the antrum. Twenty-four hours after the operation diarrhea developed, which persisted until the patient died, one week later. Culture of the stool gave a negative result. Autopsy showed widespread croupous, pseudodiphtheritic inflammation of the lower part of the ileum, as well as of the colon, with increasing intensity distally. The mesenteric vessels were patent. The peritoneal cavity contained about a liter of blood.

Their third case also involved a 55 year old man who had been subjected to subtotal gastrectomy. This was done for a duodenal ulcer and was made difficult by the presence of numerous adhesions. Six days after the operation diarrhea developed, which persisted until the man died, nine days later. Culture of the stool revealed no pathogenic organisms. Necropsy showed dehiscence of the duodenal stump with local peritonitis. In addition there was ulcerative colitis, with an ulcerative inflammatory lesion of the terminal ileum extending to the ileocecal valve.

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10. Goldschmidt, W., and Mülleder, A.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **32**:567, 1920.

In their discussion Goldschmidt and Mülleder mentioned the occurrence of similar necrotizing diphtheritic colitis following operation for tumor of the brain in 3 cases, as well as following traumatic fracture of the spinal column without operation in 1 case. Cultures of the stools in these 4 cases showed no dysentery organisms. In discussing the pathogenesis of these lesions they emphasized the alterations in intestinal flora consequent on gastric operations. This, they believed, when supplemented by peritoneal and retroperitoneal hematomas and vasomotor and vasosecretory disturbances led to the morphologic changes.

In a subsequent communication [11] they reported the occurrence of identical diphtheritic colitis in 5 patients with fracture of the spinal column. Of these, only 1 patient was operated on. Again bacteriologic examination of the stool revealed no pathogenic organisms. The presence of a hematoma of the mesentery in 1 patient led them to the belief that this predisposed to infection of the intestinal wall, which was aggravated by the vasoparalysis resulting from trauma to the spinal cord.

Within the past seven years a series of case reports have appeared in the French literature presenting observations which superficially resemble those already detailed.[12] In the main they present clinical observations without postmortem confirmation. In addition, it is to be noted that in these cases the intestinal lesion formed the primary condition and was present at the onset of the illness, so that these cases do not rightfully fall into the category with which we are concerned here.

CASE REPORTS

In a survey of the postmortem records of the Mount Sinai Hospital for the past ten years we were able to find 40 cases in which necropsy revealed pseudodiphtheritic ulceronecrotic enteritis, colitis or enterocolitis. In selecting these cases we did not include any in which the mesenteric artery or vein was thrombosed or in which there was present a diffuse vascular disease, such as periarteritis nodosa, malignant nephrosclerosis or chronic glomerulonephritis with uremia. The clinical data and pathologic material were complete in only 20 of these 40 cases. In the following case reports an attempt will be made to correlate the clinical features with the postmortem observations in an effort to indicate the pathogenesis of these lesions. The cases are typical of the entire group.

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11. Goldschmidt, W., and Mülleder, A.: Wien. klin. Wchnschr. **35**:522, 1922.

12. Moulonguet, P.: Bull. et mém. Soc. nat. de chir. **57**:1504, 1931. Castellano, G.: Policlinico (sez. chir.) **41**:175, 1934. Schwartz, A.: Mém. Acad. de chir. **62**:1239, 1936. Grégoire, R.: Bull. et mém. Soc. nat. de chir. **60**:1394, 1934; **61**: 634, 1935. de Fourmestraux, J.: Bruxelles-méd. **15**:487, 1935. Grégoire, R., and Couvelaire, R.: Apoplexies viscérales séreuses et hémorragiques (infarctus viscéraux), Paris, Masson & Cie, 1937.

CASE 1.—A 50 year old woman was admitted to the surgical service of Dr. A. A. Berg with a four month history of symptoms typical of ulcer. These had become so severe that operative intervention was decided on. A series of gastrointestinal roentgenograms showed the presence of a penetrating duodenal ulcer. A test meal showed free hydrochloric acid 48 and total acid 68. Hoffmeister's partial gastrectomy was done. The ulcer was embedded in the head of the pancreas but was dissected free and removed. On the night of the operation the patient was warm, the pulse rate was 128 beats per minute, and the blood pressure 140 systolic and 90 diastolic. Preoperatively the blood pressure was 120 systolic and 60 diastolic. Twelve hours after operation the patient began to vomit and was found bathed in sweat, with a pulse rate of 148, the pulse of poor quality. The blood pressure at this time was 70 systolic and 50 diastolic. She was given a transfusion of blood and continuous venoclysis of physiologic solution of sodium chloride, following which her condition showed distinct improvement, although she still complained of thirst. The pulse continued to be of poor quality, and the rate ranged between 140 and 150. At this time, three days after operation, the blood pressure was 125 systolic and 90 diastolic. On the next day the temperature rose to 104 F.; the pulse rate was 150 at the cardiac apex but was imperceptible at the wrist. The blood pressure dropped to 80 systolic and 60 diastolic, and the hands and feet were cold and clammy. The patient's face was pale and pinched, and she looked gravely ill. She was given 600 cc. of 10 per cent dextrose intravenously, after which the blood pressure rose to 124 systolic and 70 diastolic, and the pulse rate improved. Despite this, she rapidly became worse and died on the fourth day after operation. She had received several parenteral injections of digitan and caffeine and had had several "stimulating" enemas.

Postmortem Observations.—The peritoneal cavity contained about 200 cc. of bloody fluid. There was no evidence of generalized peritonitis. However, the duodenal stump was surrounded by an abscess cavity, which showed evidence of fat necrosis and had extended retroperitoneally to involve the right adrenal gland. The suture lines were intact. Extending from the lower portion of the sigmoid and involving the entire rectum there was a superficial greenish sloughing ulcerative membrane involving the entire circumference of the intestine and studded here and there with small hemorrhages. Microscopic examination of the involved area showed necrosis of the mucosa of the rectum, which was, however, not complete, since there were focal areas in which the deeper layers were preserved. The mucosa also showed leukocytic infiltration and deposition of fibrin, as well as surface colonies of gram-positive cocci. The submucosa was distinctly widened by edema fluid and showed focal hemorrhages. The submucosal vessels in the involved areas were dilated. The vessels outside the involved zones showed no significant changes. A lymph follicle located directly beneath the involved mucosa appeared to be without significant changes.

CASE 2.—This was the first admission to the surgical service of Dr. Richard Lewisohn of a 4½ year old child in whom abdominal pain, repeated vomiting and fever had developed about thirty-six hours previously. Examination revealed rigidity of the abdomen with tenderness and rebound tenderness. There was bilateral rectal tenderness with fulness on the right. Laparotomy disclosed a perforated appendix with generalized peritonitis. The appendix was removed. Fascial necrosis developed, which required removal of the sutures three days after the operation. At this time the general condition of the child was considered good. On the next day diarrhea developed which was attributed to the pelvic collection of pus. The child was febrile, the temperature reaching 105 F. On the

seventh day after the operation feces were noted in the wound and the abdomen became distended. Continuous venoclysis was instituted with physiologic solution of sodium chloride, and 0.5 cc. of a solution of posterior pituitary was injected intramuscularly, without relief. A Levine tube was passed, which drained off some bile-stained fluid tinged with blood. Ten days after the operation the child presented a typical peritonitic facies and a distended, silent abdomen. He was given a transfusion of 200 cc. of citrated blood. Despite this, he rapidly became worse and died in a semistuporous condition three days later.

Postmortem Observations.—The peritoneal cavity was the site of extensive though not generalized peritonitis, which caused the loops of intestines to be matted together. The entire intestinal tract was markedly dilated and showed the typical serosal reaction to peritonitis. The jejunum for the first 12 inches (30.5 cm.) beyond the ligament of Treitz was irregularly spotted with reddish purple hemorrhagic areas on its serosal surface. The mucosal surface corresponding to this discoloration was covered by a thick, coarsely granular and friable grayish yellow membrane, which extended over the rugae and troughs in an area 8 by 5 cm. The membrane was quite adherent and could be removed only with difficulty, leaving a rough surface. No other changes of importance were noted.

Microscopic examination of the involved jejunum revealed that the lesion did not involve the intestinal wall in a homogeneous fashion. There were areas of well preserved mucosa in which were well circumscribed foci of necrosis. The mucous membrane in these foci was replaced by a necrotic fibrinopurulent membrane, which extended into the submucosa. The most striking observation was the widening of the submucosa, due primarily to edema. The capillary vessels were widely dilated and blood filled, and in one area there was a focal submucosal hemorrhage. Some fibrin deposition was noted, and some infiltration by polymorphonuclear leukocytes. Several of the capillaries showed fibrin plugs. These submucosal changes extended beyond the area immediately adjacent to the foci of mucosal necrosis. The muscularis showed no significant changes. The serosa showed slight edema.

Microscopic examination of other portions of the small intestine showed no changes other than those due to the serosal reaction to peritonitis.

Case 3.—A 23 year old plumber was admitted to the medical service of Dr. B. S. Oppenheimer with a three year history of hypertension, nocturia, polydypsia and incontinence. In the year preceding his admission he had had dyspnea on exertion, as well as edema of the ankles, and had noted an increase in the size of the abdomen and increasing weakness. He had also been troubled with frequent headaches and loss of libido. Examination showed an adult man with a buffalo type of obesity, involving the head, neck and trunk but not the limbs. He appeared plethoric and had typical pig eyes, as well as striae and kyphosis. His blood pressure was 170 systolic and 130 diastolic. There was cutis marmorata. The retinal arteries were narrowed, while the veins were engorged. The penis was small and underdeveloped. Both legs presented areas of chronic ulceration. The complete investigation led to the belief that the condition was typical of the Cushing syndrome. Exposure of the pituitary gland to the action of roentgen rays was ineffective. Bilateral perirenal air insufflation yielded no information of diagnostic value. Both adrenals were therefore explored by Dr. Edwin Beer, in sequence, without a tumor being disclosed. The postoperative course was perfectly smooth until the fifth day. At this time he became incontinent, and infection of a wound developed, culture of which disclosed B. welchii. On the seventh post-

operative day he went into "vasomotor collapse," the extremities becoming cold and clammy and the pulse rapid and small. He was given a venoclysis of 500 cc. of a 5 per cent solution of sodium chloride, as well as 12 minims (0.74 cc.) of epinephrine hydrochloride and 10 cc. of an extract of adrenal cortex (Eschatin) intravenously. Despite all these measures, he failed progressively and died twenty-four hours after the onset of the collapse.

Postmortem Observations.—There was no free fluid in the peritoneal cavity. The intestines were markedly distended and heavy with a fluid content. The serosal surface of the small intestines was dull gray with a pale blue tint. In some areas the serosal vessels were engorged. The serosal surface of the colon was a dull bluish gray. The colonic mucosa was dull and lusterless and was covered by a grayish green dirty membrane which could be removed only with difficulty. This lesion was present in the ascending colon and descending colon to the sigmoid and to a much lesser extent in the transverse colon, where it consisted of areas of engorgement.

Microscopic examination of the involved colon showed focal areas of extensive mucosal necrosis with deposition of fibrin and infiltration by leukocytes. Between the glands the capillary lumens were obliterated by hyaline masses. The submucosa was irregularly widened by edema, which was most pronounced just beneath the muscularis mucosa. The veins were markedly dilated and several contained nonadherent hyaline masses. The arterioles were filled with leukocytes and showed hyalinization of their walls. The muscular layers were without significant changes. The serosa showed venous dilatation.

Case 4.—A 42 year old man was admitted to the surgical service of Dr. Harold Neuhof with a two year history of recurrent fever, cough, expectoration of nonfetid sputum and hemoptyses. A roentgenogram of the chest revealed a breaking down in the upper lobe of the left lung. Bronchoscopic examination gave negative results. Exploratory thoracotomy was therefore done, and a superficial collection of pus was found in the lung. The postoperative course was smooth for the first nine days. At this time active oozing from the lung parenchyma was noted. This was treated by packing. On removal of the packing twenty-four hours later, bleeding recurred. The temperature rose to 104 F., and the hemoglobin content dropped from 80 to 60 per cent. He was therefore reoperated on eighteen days after the first operation, and a fat-muscle transplant was placed in the pulmonary cavity. About one month later bleeding recurred, and after six days of continued oozing, which was uncontrolled by packing, it was decided to perform lobectomy. The upper lobe of the left lung was therefore ablated. The blood pressure, which had been 114 systolic and 70 diastolic on admission, did not change significantly, but the pulse rate rose immediately after operation to 156 and became irregular and almost imperceptible. The patient became irrational, and it was found necessary to "cut down" in order to institute venoclysis. He continued thus for three days and then died.

Postmortem Observations.—An ulcer, 2 by 1 cm., was observed in the antrum of the stomach, saddling the lesser curvature and extending to the submucosa. Its edges were firm, raised and injected.

The serosal surface of the jejunum and ileum was smooth and glistening. In the distal 3 feet (90 cm.) of ileum there were scattered ulcers, 1 to 2 cm. in diameter, irregular in outline and shape and covered by a shaggy greenish exudate. Many of these ulcers were situated in Peyer's patches and presented congested, slightly raised, firm edges. The ileocecal valve was not involved. No lesions were noted in the colon or rectum.

Microscopic examination of the involved ileum showed widespread focal areas of necrosis of the mucosa, between which the mucosa was preserved to varying degrees. The involved mucosa was infiltrated by leukocytes and showed deposition of fibrin as well as fibroblasts and hyaline capillary thrombi. In these areas the submucosa was markedly widened by edema and showed a large number of dilated venules and capillaries. Some arterioles showed hyaline necrosis of their walls with definite hemorrhages in several foci. There were strikingly few leukocytes in these areas of edema, in some of which deposition of fibrin had occurred. The submucosal reaction was much less marked in areas where the mucosa appeared least involved but was nevertheless distinctly recognizable. The muscular layers and the serosa were without significant alterations.

Case 5.—A 51 year old man was admitted to the surgical service of Dr. Richard Lewisohn with a ten year history of recurrent severe pain in the upper part of the abdomen, with nausea and vomiting. This had recurred ten weeks before admission and had been accompanied by sour eructations and hematemeses. A series of gastrointestinal roentgenograms revealed a deeply perforating lesion on the lesser curvature of the stomach. About three hours after the latter examination was completed, the patient suddenly experienced severe pain in the upper part of the abdomen, radiating to the left shoulder. Examination revealed the patient to be in shock and presenting marked abdominal rigidity and tenderness, most pronounced in the right upper quadrant. At operation, two and a half hours later, a perforated gastric ulcer was found and sutured. Postoperatively the patient fared poorly. He vomited repeatedly, and the abdomen was markedly distended. No relief was obtained by the use of a Levine tube or colonic irrigations. The temperature rose to 105.4 F. and the pulse rate to 120. The blood pressure showed no significant changes. Venoclysis was instituted, and epinephrine hydrochloride was given five times in doses of 5 minims. Despite this, the pulse became thready and rapid, a typical peritonitic facies developed, and the patient died five days after the operation, with a temperature of 106.4 F.

Postmortem Observations.—The peritoneal cavity showed about 1 ounce (30 cc.) of opaque yellow fluid. The intestines were markedly distended and filled with fluid. Their serosal surfaces were slightly dull, but deposition of fibrin was not noted. A Meckel's diverticulum was noted 3 feet (90 cm.) above the ileocecal valve. About a foot below the diverticulum there was an area about 3 inches (7.5 cm.) long where the ileal mucosal surface was covered by a diphtheritic membrane of greenish friable purulent material. The mesenteric border of the mucosa was not completely involved. About 1 foot (30.5 cm.) below this area an identical lesion involved about 1 foot of the intestinal wall. Just distal to this was still another patch of the same type, but smaller. The serosa in these regions was injected. The mesenteric vessels showed no gross changes. A few small red mesenteric nodes were seen. The colon and rectum showed no changes.

Microscopic examination of the involved ileum showed that the mucosal necrosis was focal in distribution and of variable severity. Where necrosis had occurred, the mucosa was replaced by a necrotic cellular débris, enmeshed in fibrin. In these areas the muscularis mucosa was involved in the process. The submucosa was markedly thickened by edema and some increase of connective tissue. The capillaries were widely dilated. There was no striking increase in cellular content in areas which were not severely involved in the necrosis. In the areas of lesser involvement the lesion did not extend to involve the muscular layers. In the more severely involved areas the process involved the muscularis down to the serosa, which showed some edema and cellular infiltration.

Histologic changes of the sort observed in these cases are certainly unusual and bear little resemblance to the usual inflammatory lesions found in the small or large intestines. We may perhaps best portray the lesions by a survey of the histologic changes in the entire group of cases which we have studied and thus reconstruct the various stages of their development.

Lesions in the earliest stages, found at a short distance from those in the more advanced stages or even in no relation to a lesion in an advanced stage, present as their most striking feature marked dilatation of the capillaries and venules, which may be so large as to distort the normal relationship of the tissues. This alteration occurs primarily in the submucosa but in a somewhat later stage is also found in the mucosa, where the sinus-like venous dilatation distorts the villi. This may occur in regions where the mucosa is apparently intact and therefore we feel that it represents an early stage of the process. Somewhat later there is noted, in addition to the aforementioned widening of the vessels, a widening of the stroma of the submucosa and mucosa by edema. The latter is strikingly poor in cellular content in its earlier phases but is frequently associated with focal hemorrhages in the immediate neighborhood of the distended vessels. These hemorrhages are found not only in the submucosa but in the villi as well. There is no apparent loss of continuity of the vessel walls, and one gains the impression that the extravasation is the result of diapedesis from a dilated capillary or venule in which stasis has occurred. In addition to these changes in the presence of well preserved mucosa, the progress of the lesion appears in alterations of the columnar cells which line the villi. The lining epithelium (at the onset usually only the portions at the tips of the villi) shows loss of nuclear staining and eventually the typical picture of necrosis (fig. 1 *A* and *B*). This, it must be emphasized, begins at the tips of the villi and is found in the presence of well preserved mucosa at the bases of the villi as well as between these. The necrotic areas of mucosa show focal desquamation. With the extension of the process, the necrosis involves the deeper layers of the stroma, beneath the mucosal cells, and may penetrate through the muscularis mucosa to involve the submucosa (fig. 2). With the progress of the lesion there is replacement of the mucosa by a membrane consisting of necrotic cellular débris enmeshed in fibrin. As the lesion progresses, leukocytes appear in the edematous stroma until eventually the appearance of typical purulent inflammation is created. It is impossible to evaluate the relative importance of infection from the intestinal lumen and of the presence of the necrotic mucosa in the causation of the latter reaction.

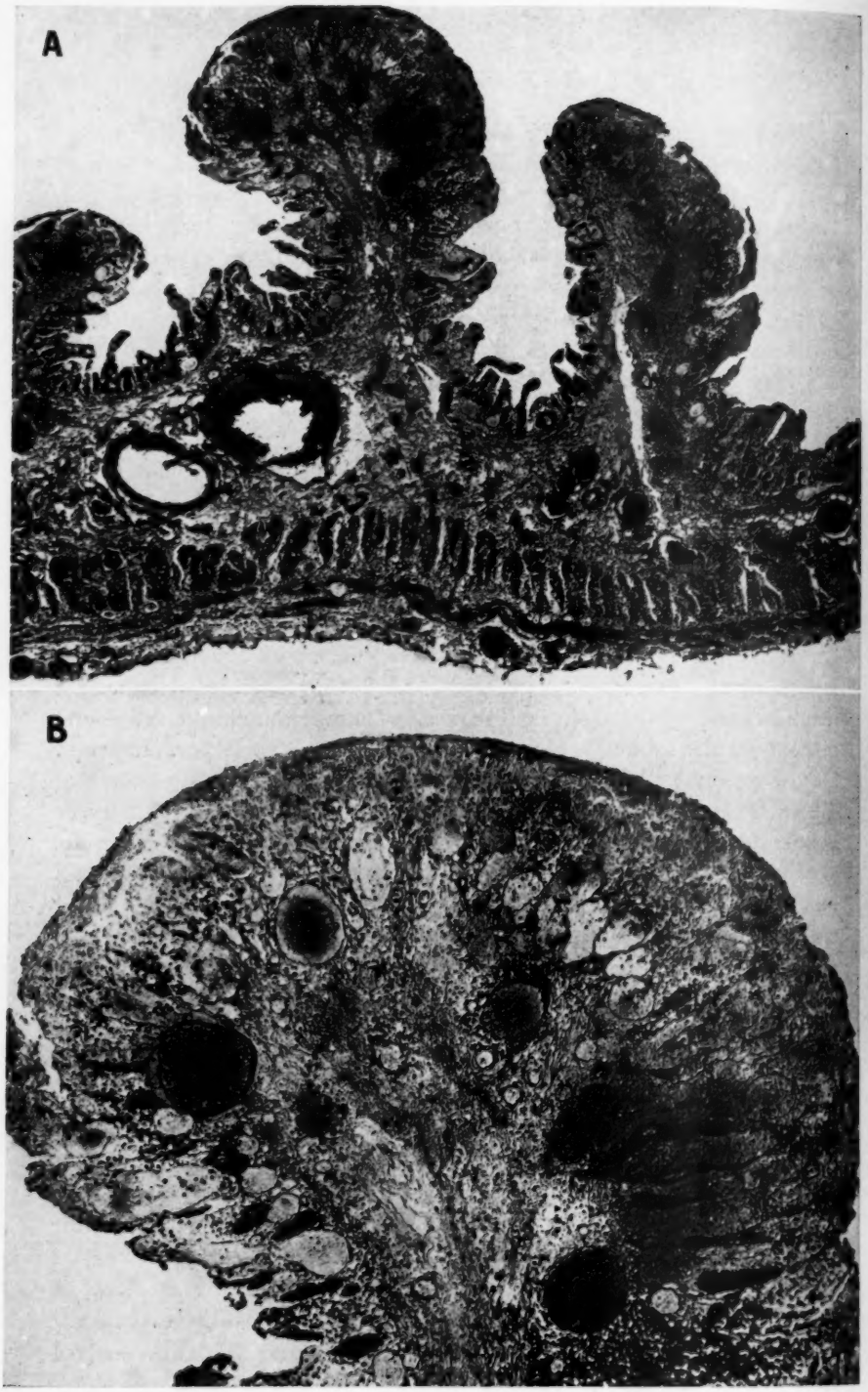

Fig. 1.—*A*, section of jejunum showing early necrosis of the tips of villi with well preserved mucosa at the bases. Widening of the submucosa, congestion and dilatation of the venules and capillaries, and interstitial edema can be observed.

B, the same section under higher power, to demonstrate the early necrosis of the tips of villi. Note the absence of primary cellular infiltration.

In the later stages of the process hyaline thrombi appear in many of the smaller vessels. In addition, in some instances, a striking inverse relationship is observed between the caliber of the arterioles and that of the capillaries and venules. In addition to the hyaline thrombi mentioned we have observed an occasional thrombus adherent to the wall of a vessel and containing leukocytes. One instance, at least, we observed, in which the inflamed submucosa showed the presence of fibroblasts.

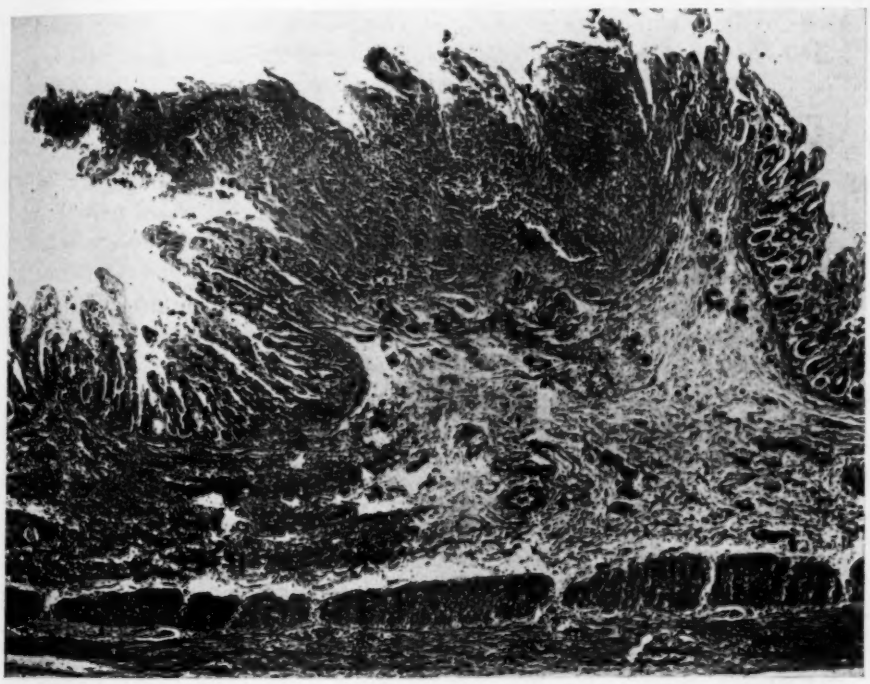

Fig. 2.—Section of ileum showing focal mucosal necrosis and ulceration with submucosal reaction.

While in the majority of instances the process was restricted to the mucosa and submucosa, an occasional extension to the muscular layers was noted, so that it is apparently possible for the entire intestinal wall to be involved. Despite this, bacterial stains revealed organisms only on the mucosal surface.

The focal nature of the process is well shown by the fact that in a mucosal lesion that occurred in the duodenum Brunner's glands in direct contact with the involved mucosa showed no significant changes. In a similar lesion partial necrosis of Brunner's glands occurred. Similarly, in the colon it was observed that solitary lymph follicles which

were in direct contact with the necrotic mucosa were without significant changes. In other lesions the process involved the follicles also. These observations are of special significance when it is recalled that the solitary follicles, as well as Brunner's glands and the intestinal villi, receive their blood supply from totally separate arteriolar branches of the same submucosal artery.[13]

COMMENT

An investigation of the data on our material reveals that we have been dealing with a wide variety of clinical conditions. Among these are to be noted the following: gastric lesions, necessitating gastrectomy; perforation of a gastric ulcer; carcinoma of the lung with bleeding, requiring lobectomy; acute appendicitis with peritonitis; bilateral exploration of the adrenal glands, and, in addition, hepatic cirrhosis with hemorrhage, and extensive burns. Despite the wide variety of conditions, an analysis of the clinical data revealed that shock had been present in each instance and that it was usually present in direct relation to the few observed clinical signs of the intestinal lesion which we are discussing. This is true not only of our material but also of those cases reported in the literature the data on which are sufficiently complete to permit evaluation.[14]

The foregoing considerations led us to inquire into the possible processes whereby the vascular mechanisms involved in shock could be responsible for a lesion such as the one described. It will be recalled that this lesion is distinguished by the presence of dilated, usually blood filled venules and capillaries, early, relatively acellular submucosal and mucosal edema, pericapillary hemorrhages and finally focal mucosal necroses which by fusion, extension and secondary infection give rise to the more extensive pseudomembranous lesion.

At the present time it is widely accepted that the vascular mechanisms involved in shock serve the useful "purpose" of causing redistribution of blood so as to preserve the functions of organs absolutely necessary for life.[15] Basically, this involves alteration of the volume capacity of the cardiovascular system in adaptation to a decrease in the volume of effectively circulating blood. The mechanisms effecting this adaptation constitute the characteristic vasomotor response seen in shock. That these mechanisms do not function uniformly throughout

13. Patzelt, V., in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1936, vol. 3.

14. (*a*) Ewig, W., and Klotz, L.: Deutsche Ztschr. f. Chir. **235**:681, 1932. (*b*) Riedel.[8] (*c*) Bierende.[9] (*d*) Goldschmidt and Mülleder.[10]

15. Cannon, W. B.: Physiol. Rev. **9**:399, 1929.

the body was indicated in the work of Gesell,[16] who showed that with decrease in blood volume of only 10 per cent there was simultaneous decrease of more than 60 per cent in the blood flow through the submaxillary gland. This occurred despite rise in blood pressure and was attributed to widespread vasoconstriction. The latter mechanism had been considered as the bodily response to shock as far back as 1879 by Mapother,[17] who based his explanation entirely on clinical observations. In this he was supported by Malcolm,[18] who noted the extreme pallor of the peritoneal surfaces in shock and made the observation that the arteries were empty while the venous trunks were full. The widespread increase in peripheral resistance caused by the vasoconstriction consequent on shock [19] is not equally manifest in all organs. The work of Rein and his co-workers [20] and of Blalock and Levy [21] showed that the vasoconstriction is most marked in the tissues which at the moment of application of the constricting stimulus are least active. This constriction may occur in the absence of rise in blood pressure and hence must be associated with compensatory vasodilatation elsewhere in the body. This vasodilatation is partially the result of local formation in actively functioning tissues of various metabolites that are effective in counteracting the vasoconstrictor stimulus.[22] These observations serve partially to explain the occasional vasodilatation in response to epinephrine. Rein and Rössler [20d] in one of their experiments were able to demonstrate that a loss of blood amounting to 2 per cent of the body weight in a dog resulted in a 20 per cent drop in blood pressure in eight minutes. Simultaneously the flow through the intestine decreased 70 per cent while that through the femoral artery dropped 62 per cent and that through the inferior vena cava 15 per cent. Ten minutes after cessation of the bleeding the blood pressure, after a preliminary further drop, rose to within 5 per cent of its previous value, the peripheral blood flow through the femoral artery rose to 30 per cent above its initial value, while the intestinal blood flow rose very much more slowly to a value which was 20 per cent below its original state. An interesting feature of this work lies in the demonstration that the vessels of

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17. Mapother, E. D.: Brit. M. J. **2**:1023, 1879.

18. Malcolm, J. D.: Tr. M. Soc. London **32**:274, 1909.

19. Erlanger, J.; Gesell, R., and Gasser, H. S.: Am. J. Physiol. **49**:90, 1919.

20. (*a*) Rein, H.: Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch. **10**:27, 1937. (*b*) Rein, H., and Mertens, O.: Arch. f. d. ges. Physiol. **237**:231, 1936. (*c*) Mertens, O.; Rein, H., and García Valdecasac, F.: ibid. **237**:454, 1936. (*d*) Rein, H., and Rössler, R.: Ztschr. f. Biol. **89**:237, 1929.

21. Blalock, A., and Levy, S. E.: Am. J. Physiol. **118**:734, 1937.

22. Gaddum, J. H.: Gefässerweiternde Stoffe der Gewebe, Leipzig, Georg Thieme, 1936.

the kidneys participate in the general vasoconstriction to a minimal degree.[23] It requires about one hundred times as much epinephrine to produce vasoconstriction in the kidneys as in the peripheral muscles. Of utmost importance in this connection is the fact that this vasoconstriction occurs as the first overt manifestation of the vasomotor response which is the body's reaction to the shocking stimulus, whether this is loss of blood,[16] loss of body fluid [24] from the blood stream into the tissues or loss from the blood stream via the kidneys,[25] or painful stimuli.[26] In the final analysis we find that vasoconstriction may be considered compensatory for the marked discrepancy between the blood volume and the capacity of the cardiovascular system; or, as will be shown later, it may be one part of a vicious circle that causes loss of body fluid into the tissues. This concept reveals the fundamental harmony between the views of O'Shaugnessy [26b, c] and Blalock.[24]

The primary vasoconstrictive reaction does not and cannot persist indefinitely. It may be terminated by the passing of the shock stimulus. Under these circumstances the patient presents the picture of what may be called "compensated shock." [14a] On the other hand, the vasoconstriction may disappear as a result of local tissue changes caused by the local ischemia which it creates [27] despite the persistence of the shock stimulus. There results an "outlying acidosis due to functional ischemia," [27a] which experimentally has been produced by injection of hypertonic dextrose or mechanical interference with the circulation. This has been known for a long time to be able to cause vasodilatation.[28] Aside from this, other metabolites capable of producing the same reaction are formed and undoubtedly participate in this process.[29]

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25. Keith, N. M.: Am. J. Physiol. **68**:80, 1924.

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A further consequence of the vasoconstriction and the associated anoxemia of tissue is a drop in the gradient of pressure within the capillaries. This, together with the anoxemia, leads to an increase in the permeability of the capillary endothelium,[27c] so that, whereas the latter formerly retained about 95 per cent of the total plasma protein, it loses its power to do this. As a result there occurs a transudation of the plasma protein into the tissue spaces. This is at first not accompanied by passage of the cellular components of the blood since in the earlier phases of this reaction, experiment has shown, the transudation of fluid is still directly proportional to the difference between the capillary pressure and the effective osmotic pressure of the plasma proteins. This observation apparently indicates that the capillary endothelium is still acting as a passive filter, though it is more permeable than usual.[27c] Furthermore, this process is reversible if the lack of oxygen is of sufficiently brief duration. With persistence of the anoxemia and continuous loss of plasma protein into the tissue spaces a vicious circle starts, since reduction of the blood volume follows which in itself may cause vasoconstriction. In addition, the loss of blood plasma decreases the effective osmotic pressure of the intravascular contents and thus tends to increase the outflow of plasma. This concentration of the blood is invariably present in shock.[30]

Further prolongation of the anoxemia of the capillary wall results in further changes in the capacity of the wall to retain the vessel contents. The cellular components and formed elements become increasingly concentrated, and the capillary wall itself becomes more "sticky" (Krogh, quoted by Landis [27c]). The morphologic component of these

30. (*a*) Darrow, D. C., and Buckman, T. E.: Am. J. Dis. Child. **36**:248, 1928. (*b*) McIntosh, R.; Kajdi, L., and Meeker, D.: J. Clin. Investigation **9**:333, 1931. (*c*) Gibson, J. G., and Kopp, I.: ibid. **17**:219, 1938. (*d*) Rogers, F. T.: Proc. Soc. Exper. Biol. & Med. **38**:73, 1938. (*e*) Romberg, E.; Pässler, H.; Bruhns, C., and Müller, W.: Deutsches Arch. f. klin. Med. **64**:652, 1899. (*f*) Underhill, F. P.; Kapsinow, R., and Fisk, M. E.: Am. J. Physiol. **95**:302 and 325, 1930. Underhill, F. P., and Fisk, M. E.: ibid. **95**:330, 1930. (*g*) Davidson, E. C., and Matthew, C. W.: Arch. Surg. **15**:265, 1927. (*h*) Underhill, F. P.; Carrington, G. L.; Kapsinow, R., and Park, G. T.: Arch. Int. Med. **32**:31, 1923. (*i*) Harkins, H. N.: Proc. Soc. Exper. Biol. & Med. **32**:432, 1934 (*j*) Olivecrona, H.: Acta chir. Scandinav. **54**:559, 1922. (*k*) Lundgren, A. G. H.: ibid. (supp. 39) **77**:1, 1935. (*l*) Chang, H. C.; Harrop, G. A., and Schaub, B. M.: J. Clin. Investigation **5**:407, 1928. (*m*) Peters, J. P.; Kydd, D. M., and Eisenmann, A. J.: ibid. **12**:355, 1933. (*n*) Scott, H. G.: Arch. Surg. **36**:816, 1938. (*o*) Stewart, J. D., and Rourke, G. M.: J. Clin. Investigation **17**:413, 1938. (*p*) White, J. C.; Whitelaw, G. P.; Sweet, W. H., and Hurwitt, E. S.: Ann. Surg. **107**:287, 1938. (*q*) Gatch, W. D., and Little, W. D.: J. A. M. A. **83**:1075, 1924. (*r*) White, J. C.; Sweet, W. H., and Hurwitt, E. S.: Ann. Surg. **107**:438, 1938. (*s*) Riessinger, H., and Schneider, H.: Deutsche Ztschr. f. Chir. **217**:303, 1929. (*t*) Ewig and Klotz.[14a]

functional changes is seen in the formation of capillary thrombi, observed in our material as well as in that studied by Bierende.[9] A further consequence is seen in the appearance of hemorrhages which, in the absence of any morphologically demonstrable lesion of the vessels themselves, are attributed to diapedesis.

It is but a short step from the foregoing events to the appearance of the tissue necrosis which was seen to occur in our cases. That such a process may occur in shock has been known since 1906, when Elliott [31] observed necrosis in the intestinal tract after bilateral adrenalectomy. Since then it has been repeatedly mentioned as an incidental observation at autopsy in experimental animals used in the study, directly or indirectly, of the phenomena of shock.[32] The exquisitely focal nature of the lesions can be understood from the nature of the vascular mechanisms involved and from the anatomic distribution of the blood supply to the intestines as described in a foregoing paragraph. Thus the close juxtaposition of necrotic mucosa and well preserved Brunner's glands of submucosal lymphoid follicles is no surprise. The phenomena involved in the vasomotor reactions also make it readily understandable that the lesion which is created should take its origin within the wall of the intestine, i. e., in the submucosa, rather than on its surfaces.

We are not in a position to evaluate the importance of infection of the intestinal wall by the bacterial flora of the lumen. That infection occurs is evidenced by the purulent nature of the later stages of the lesion. That this is a late manifestation is indicated by its absence in the earliest phases of the lesion. In keeping with this is also the sudden rise in systemic temperature which so frequently terminated life in our material.

SUMMARY

A review of the literature of acute postoperative ulcerative and diphtheritic enteritis is presented. A survey of the postmortem records of the Mount Sinai Hospital for the last ten years revealed 40 cases in which necropsy showed this lesion. In the selection of cases we avoided any in which the mesenteric vessels were thrombosed or in which a diffuse vascular disease was present. Intestinal diseases of known cause,

31. Elliott, R. T.: J. Physiol. **49**:38, 1914. Elliott, R. T., and Tuckett, I.: ibid. **34**:332, 1906.

32. Freeman, N. E.; Shaffer, S. A.; Shecter, A. E., and Holling, H. E.: J. Clin. Investigation **17**:359, 1938. Unterberger, S.: Arch. f. exper. Path. u. Pharmakol. **2**:89, 1874. von Mering, J.: ibid. **13**:86, 1881. Saikowsky: Virchows Arch. f. path. Anat. **37**:346, 1866. Kebler, F.: Arch. f. exper. Path. u. Pharmakol. **9**:137, 1878. Elbe, D.: Virchows Arch. f. path. Anat. **182**:445, 1905. MacNider, W. de B.: J. Exper. Med. **27**:519, 1918. Heubner, W.: Arch. f. exper. Path. u. Pharmakol. **56**:370, 1907. Moon, V. H., and Kennedy, P. J.: Arch. Path. **14**: 360, 1932. Keith.[25] Romberg and others.[30e] Elliott.[31]

such as typhoid and dysentery, were likewise excluded. Five typical cases are reported in detail.

A survey of the histologic observations in our material permits us to reconstruct the pathogenesis of the lesion as follows: The earliest change consists in marked distention of the capillaries and venules, first in the submucosa and subsequently in the mucosa. This is followed by marked submucosal edema and occasional focal hemorrhage in the vicinity of the distended vessels (diapedesis). The arterioles frequently appear to be contracted. The next change consists in focal necrosis of the mucosa, frequently limited at first to the tips of the mucosal folds. With advance of the lesion the areas of mucosal necrosis spread and fuse. The necrosis extends through varying depths of the intestinal wall, although in most cases not beyond the submucosa. In the advanced stages, the necrosis is accompanied by an inflammatory cellular reaction, and hyaline thrombi are seen in many of the smaller vessels. The focal nature of the lesion is striking.

An analysis of the records showed that the lesion was present in a wide variety of clinical conditions. It appeared consequent to operative procedures in the abdomen, as well as after lobectomy, and it appeared in patients who had not undergone any operative procedures but were suffering from extensive burns and gastrointestinal hemorrhage. The one finding that was present in all the cases was shock.

We have reviewed the literature on the vasomotor mechanisms involved in shock and have discussed these in relation to the evolution of the lesion described and noted a similar lesion following experimental production of shock by a variety of methods.

CONCLUSION

From a study of 40 cases in which necropsy showed acute ulcerative or diphtheritic enteritis and from a review of similar cases in the literature we have concluded that the vasomotor mechanisms known to occur in shock are responsible for this lesion. Shock was present in all the cases studied, and a similar lesion has been observed following experimental production of shock.

CONGENITAL ABSENCE OF THE PENIS

GEORGE J. RUKSTINAT, M.D.
AND
ROBERT J. HASTERLIK, M.D.
CHICAGO

Congenital absence of the penis, according to Harris,[1] occurs in 1 of 30,000,000 persons. In the fifty years preceding 1898 it was encountered as follows: once each in England, France, Germany and Austria, and twice in the United States. In the last forty years 9 more instances were recorded. In at least 4 of these 15 instances the condition might be classified as hermaphrodism or scrotal penis. Excluding cases of epispadias, hermaphrodism and scrotal and perineal penis, one finds only 10 incontrovertible reports of congenital absence of the penis.

Steckmetz [2] published his findings in a 3 month old child whose penile site on the mons veneris was occupied by a furrowed elevation, 10 by 5 mm. In the subcutaneous tissue of the scrotum was a smegma-covered glans penis with a well formed foreskin. The shaft was rudimentary. A perineal midline structure was 10 mm. high and 3 mm. wide and resembled a rooster's comb. It was highest close to the anus but not connected with it. The rectum contained a small nubbin close to the sphincter on the anterior wall, into which the urethra opened. Göschler's [3] patient, a 27 year old man, had orchitis but lacked a penis. On the perineum was a warty mass, 3.8 cm. long and 1.8 cm. wide and high. This contained erectile tissue, which had been stimulated first when the patient rode bareback. The man subsequently produced friction on this tissue with a stick or the edge of a chair to obtain sexual satisfaction. The urethra emptied into the rectum and was 3.8 cm. long. In Räuber's [4] case approximation of the rectum and urethra was noted; part of the penis existed ectopically. His patient, a man 38 years old, lacked a penis in the usual position and passed urine through the rectum. Marked irritation from the urine had been noted for about twenty years. This was so severe at times that the man applied

From the Norman Bridge Pathological Laboratory, Rush Medical College of the University of Chicago.

1. Harris, R. P.: Philadelphia M. J. **1**:71, 1898.
2. Steckmetz, F.: Beitr. z. klin. Chir. **17**:398, 1896.
3. Göschler: Vrtljschr. f. d. prakt. Heilk. **63**:89, 1859.
4. Räuber: Virchows Arch. f. path. Anat. **121**:604, 1890.

hot poultices for relief and on occasion sat on ice. The penile elements present were incorporated in the anterior wall of the rectum. Passion manifested itself in a tickling sensation in the rectal wall and was accompanied by a seminal discharge into the bowel.

The irritating effect of urine on the rectum and probable ascending urinary infections were major complications in 2 patients: Räuber's [4] and Mathews'.[5] The latter was consulted by a 30 year old man who had no penis but had a well developed scrotum and large testes. The urethral opening was 2.5 cm. cephalad to the anal sphincter, on the anterior rectal wall. The rectal mucosa was ulcerated extensively and beset with hemorrhoids. Defecation and urination were painful, although some relief was obtained after massage of the hemorrhoids. The irritant effect of urine on the rectum of an adult contrasts with its innocuous effect in a child. Nélaton [6] and Collier [7] reported congenital absence of the penis with a urethral opening in the rectum in infants. The bowel movements of these patients were more liquid than normal but apparently the bowel wall was unaltered. Both adults who complained of rectal pain had fever, chills and sweats at various times and possibly suffered from cystitis or ascending urinary infection. Mathews' patient died of renal disease, supposedly uremia, about six months after the massage of hemorrhoids, mentioned. The 13 year old boy whose case was reported by Drury and Schwarzell [8] has a urethral opening similar to that of the men discussed but has escaped rectal difficulties.

In the foregoing review the penile anomalies were grouped so that one might trace the stages of posterior urethral recession. The various urethral openings were noted anteriorly as in epispadias, perineally, anally and rectally in progressive steps. The most marked stage of maldevelopment is complete closure of the large bowel distally, with or without the presence of an anus or a vesicorectal fistula. These complicated anomalies are compatible with intrauterine life only and have been reported in newborn infants by Magid,[9] Priesel [10] and Feller and Sternberg.[11] Outstanding characteristics of this group are: absence of the penis, prostate gland and urethra; retention of one or both testes in the abdomen; termination of the rectum in a fibrous strand; a connection between the large bowel and the bladder by way of a patent channel

5. Mathews, J. M.: Am. Practitioner & News **17**:27, 1894.
6. Nélaton, A.: Gaz. d. hôp. **27**:45, 1854.
7. Collier, J., cited by Harris.[1]
8. Drury, R. B., and Schwarzell, H. H.: Arch. Surg. **30**:236, 1938.
9. Magid, M.: Monatschr. f. Geburtsh. u. Gynäk. **83**:63, 1929.
10. Priesel, A., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1931, vol. 6, pt. 3.
11. Feller, A., and Sternberg, H.: Ztschr. f. Anat. u. Entwcklngsgesch. **108**: 282, 1938.

or a fibrous union; ureteral stenosis or cystic distal termination; cystic changes of the kidneys, and bony deformities, notably a narrow pelvis and vertebral imperfections. This group, though small, has been helpful from an embryologic and physiologic standpoint. It had been assumed formerly that urine from the fetus contributed to the liquor amnii. Monstrosities lacking a urethral exit could not furnish urine to the liquor, yet in all instances the amounts of liquor bathing the child were normal. The bony deformities found in these bodies represent a stage only slightly above that of sympodia or of sirenoid monsters.

The following report of a case illustrates the several genitourinary anomalies and associated skeletal defects.

REPORT OF A CASE

A prematurely born white boy, 41 cm. long and weighing 2,020 Gm., was born by single footling breech presentation to a 19 year old mother after an uneventful forty hour labor. The baby did not cry or breathe and showed evidences of asphyxia. There was complete absence of the penis and anus externally (fig. 1), their normal sites being marked by smooth areas similar to the contiguous skin. The scrotum was 2 cm. in diameter and located in the normal position; its integument was wrinkled and pink-gray. No raphe was visible on the scrotum or on the perineum (fig. 1). The left foot was rotated and deformed so that its sole faced the median sagittal plane of the body. The right foot was normal. The toe nails reached to within 2 mm. of the ends of the great toes. No changes from the normal were observed in the skin, which was covered with fine lanugo hair.

The internal organs after fixation in a 4 per cent solution of formaldehyde disclosed the bladder, 1 by 3 by 1 cm.; in its wall, which was thickened to 4 mm. at its anterior superior border in the midline, was a nubbin of tissue, 12 by 5 mm., projecting superiorly from the wall, which represented a blunt closed urachus. At the right inferior posterior portion of the bladder externally, the distal end of a hugely dilated colon joined the wall of the bladder (fig. 3). Inferior and posterior to this anastomosis, the right ureter entered the bladder. At the corresponding point on the left side the left ureter made its entry (fig. 4). There was no urethral orifice in the bladder.

The testes with their epididymes measured 1.4 by 1.4 by 0.4 cm. and appeared grossly normal. The left was in the scrotum; the right lay on the left psoas at its midportion. The ductus deferens of each side became lost in a mass of fibrous and areolar tissue near the site of entrance of the ureters into the bladder. No prostate gland or seminal vesicles were found.

The right kidney was 8 by 10 by 7 mm.; its surface was knobby and cystic. The right ureter pursued a very tortuous course to its junction with the bladder. It measured up to 3 mm. in diameter externally, its wall was thickened markedly up to 1 mm., and in most places the lumen was of pinpoint size. The left kidney was 15 by 12 by 10 mm. Its surface was deformed markedly by cysts up to 6 mm. in diameter. The ureter 4 mm. distal to the ureteropelvic junction became a thin fibrous strand, 0.5 mm. in diameter, extending 8 mm., and again widened out into a more normal-appearing ureter, 2.5 mm. in external diameter.

The normal-appearing cecum and appendix lay in the right lower quadrant of the abdomen, as did the distal end of the gastrointestinal tract. The large bowel

measured 35 cm. from the cecum to its distal termination in the bladder. Immediately distal to the cecum the colon was 15 mm. in circumference, and the folds of the mucosa were very prominent. The colon 15 cm. distal to the cecum began progressively to balloon into a thin-walled structure, 55 mm. in circumference, with a wall 0.5 mm. thick. The mucosal surface here was smooth and without folds. Meconium was present in the distal 15 cm. of bowel. At its junction with the bladder the colon tapered abruptly to a point. A flap of the mucosa of the

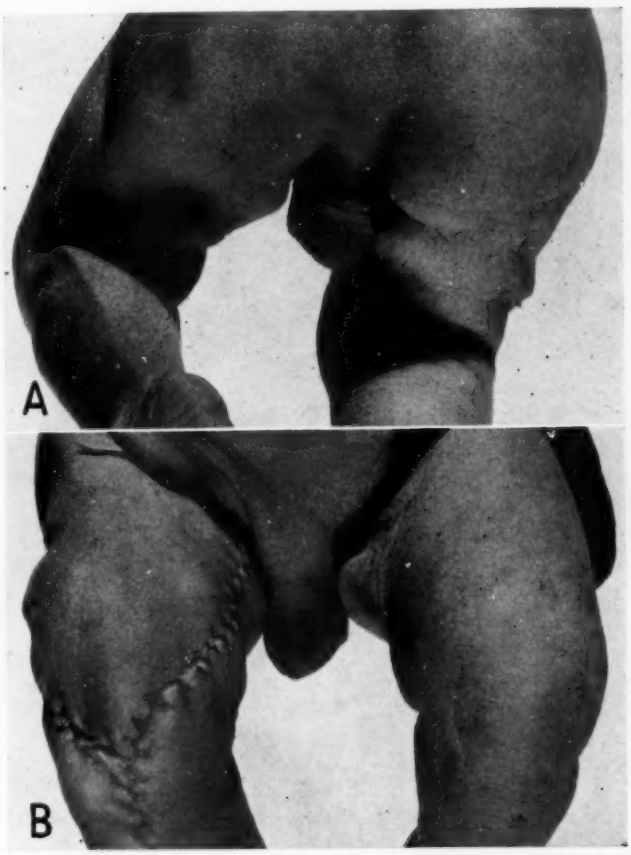

Fig. 1.—*A*, posterior view illustrating the absence of the anus and of the scrotal raphe clubfoot on the left. *B*, anterior view demonstrating the absence of the penis and of the scrotal raphe.

bladder formed a valvelike structure which partially covered the opening of the colon into the bladder. This communication between the bladder and the colon was patent.

Two umbilical arteries and one umbilical vein were present. The left umbilical artery pursued a very tortuous course about 2 cm. before entering the umbilical cord.

The spinal column showed no obvious gross defects other than a deviation of the last few coccygeal segments toward the left. Roentgen examination of the spine revealed displacement of several ossification centers of the transverse processes of the fifth lumbar and first three sacral vertebrae.

The ilia showed no significant changes; the acetabulums appeared normal.

The inferior rami of the ischia were displaced medially and fused in the midline below the true symphysis pubis along the greater part of their course, forming what appeared to be a greatly elongated symphysis pubis, 28 mm. long. At a 50

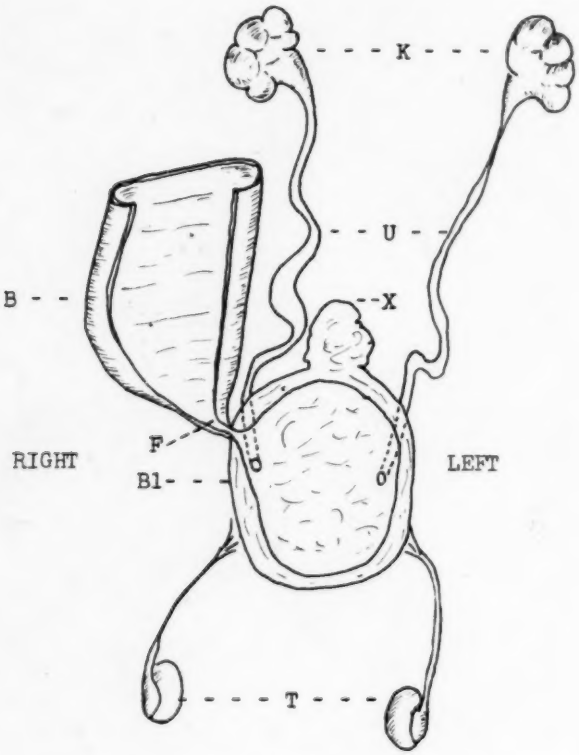

Fig. 2.—Schematic representation of anatomic relation. *B* indicates the bowel; *Bl*, the bladder; *T*, the testes; *U*, the ureters; *K*, the kidneys; *X*, the urachus, and *F*, the communications between the bowel and the bladder.

degree angle, where the ischia separated, were the ischial tuberosities, which at their greatest point were separated by a distance of only 12 mm. The distance between the ischial spines was 12 mm. also. From the tip of the coccyx to the point of bifurcation of the medianly fused inferior rami of the ischia, the anterior-posterior diameter of the outlet of this pelvis was 10 mm.

There was no asymmetry of the brain. No changes were observed in the hypophysis or in the large cranial venous sinuses. The cranial fossae were symmetric. The tongue, pharynx, larynx and roof of the mouth were normal.

Histologic Observations.—In the paraffin sections the right kidney, fixed in a 4 per cent solution of formaldehyde and stained with hematoxylin and eosin, hugely dilated veins occupied about 20 per cent of the section, had remarkably thin walls and were associated with distended tortuous capillaries. At least one third of the section consisted of old connective tissue, partly hyalinized and sparsely sprinkled with small lymphocytes. Localized clumps of 50 to 100 of these cells were scattered sparsely throughout the section. The arteries had thick walls (fig. 5), some of which were twice as thick as their lumen. At least half of this increased

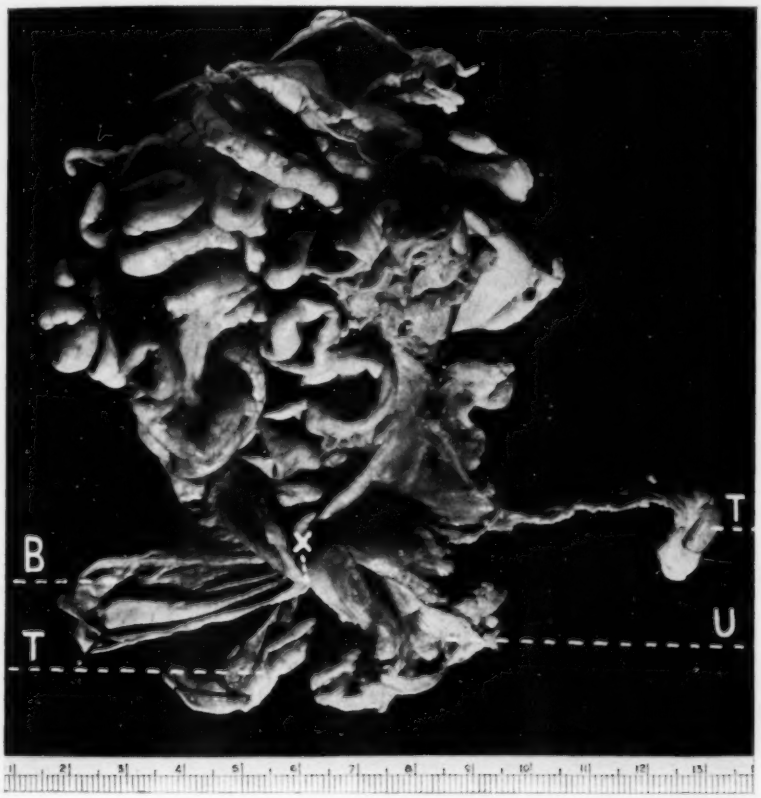

Fig. 3.—Anterior view of the pelvic and abdominal contents, illustrating at *B* the dilated part of the large bowel, at *U* the urinary bladder, at *T* the testes and at *X* the communication of bowel and bladder.

thickness was due to edema. Most of it was in the media, with the adventitia also involved. Collecting tubules occurred singly or in groups up to seven and were lined by high cuboidal epithelium. The cysts were irregular, lined by a compressed single layer of epithelial cells. Their bulk occupied about 30 per cent of the section; all the cysts were empty. No structures resembled glomeruli, but occasional partially hyalinized bodies suggested degenerated and organized glomeruli as in advanced nephrosclerosis.

In the left kidney glomeruli occurred, 5 to 8 per square millimeter. They were most numerous in two sharply circumscribed regions, each about 3.5 by 3 mm. Closely packed masses of epithelial cells were seen, concentrically layered or in a heterogeneous arrangement.

In both kidneys dilated tubules, especially outside of the fibrous snared-off regions, contained amorphous débris, in which were green globules resembling bile. At least three fourths of the cells within these tubules were lymphocytes. Only rare polymorphonuclear leukocytes and other inflammatory cell types occurred. In several regions, green globules with tan débris were observed in the walls

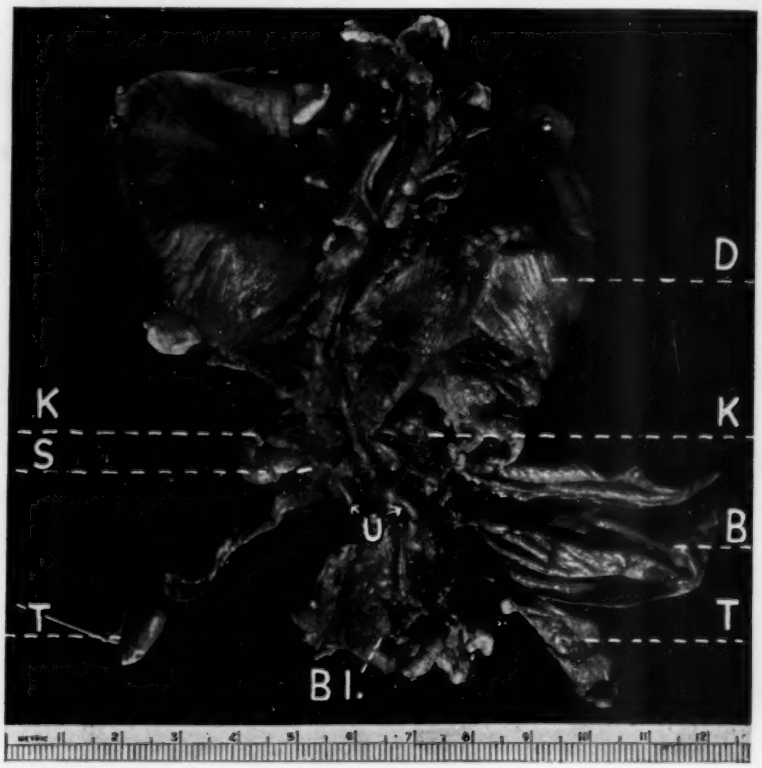

Fig. 4.—Posterior view of a dissection illustrating at *D* the diaphragm, at *U* the ureters, at *S* the ureteral stricture on the left, at *K* the kidneys, at *B* the dilated bowel, at *Bl* the urinary bladder and at *T* the testes.

of the blood vessels and in the connective tissue outside the tubules. A typical region showing the latter type of accumulation had a central area of necrosis, then a zone of sparsely applied fibroblasts and at the periphery collections of lymphocytes with fibroblasts.

Each cross section of testicle consisted about one-half of red blood cells free in the interstitial tissue. There was blood free in the tunica albuginea. In the epididymis there were lymphocytes in the loose connective tissue between the tubules, in irregular rows. They comprised about 10 per cent of the cells seen. There was extensive desquamation of the cells lining the tubules.

A section of urinary bladder close to the left ureteral orifice had a heavy muscular wall. The lining of the bladder was vacuolated extensively and consisted of four to five rows of transitional epithelium. In the first part of the left ureter the cell layers numbered up to eight. Only occasional scattered lymphocytes were observed in the submucosa of the bladder. The wall of the right vas deferens was twice the normal thickness and edematous. There were numerous lymphocytes, especially in the zone adjacent to the wall of the bladder.

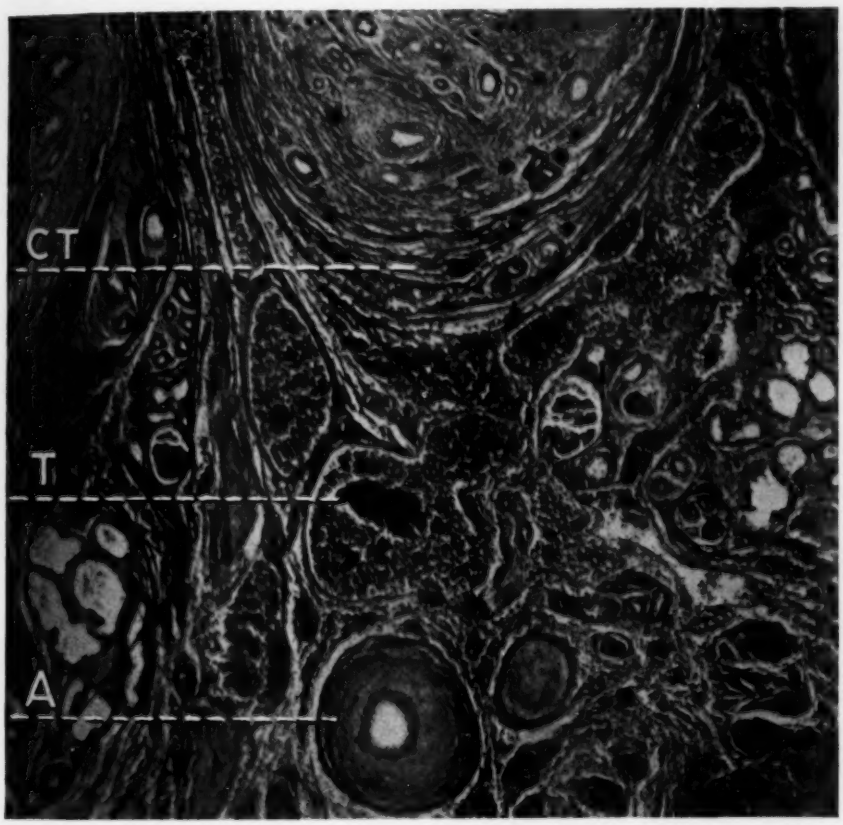

Fig. 5.—Low power photomicrograph of a section of the left kidney, illustrating at *A* a thickened artery, at *T* dilated tubules filled with débris, bile and lymphocytes and at *CT* the connective tissue bands enclosing hyalinized renal glomeruli and tubules.

A section of the fibrous mass in the region of the urachus was bladder with a wall as muscular as in the other sections and with an unaltered lining. Green globules, like those in smears of fresh meconium and in the dilated débris-filled tubules of the kidney, were seen in an unstained section of the kidney.

Sections of other internal organs revealed no pathologic changes pertinent to this problem.

COMMENT

An analysis of the conditions encountered in the present report corroborates Hinman's [12] opinion: "Malformations of the penis usually are associated with other anomalies, very often of the urethra. They are caused by maldevelopment of the phallus and genital tubercle, together with those portions of the urogenital sinus concerned in the formation of the external genitalia and urethra." The complete absence of the anus and rectum, however, further complicates the embryologic distortions. The absence of a perineal and scrotal raphe suggests a midline defect in early embryonic development. To produce the picture presented here, the cloaca must have failed to form the distal part of the bowel and contributed only the urinary bladder, omitting the proximal part of the urethra. The urogenital sinus, which normally contributes the rest of the urethra, failed to function, as did the genital tubercle, which should have differentiated into the penis and the genital folds which ordinarily form the prepuce and integument of the penis. The lateral genital swellings united to form the scrotum, which lacked only a raphe.

The acetabulums were deep and thin; they appeared disproportionately large in the narrow pelvis. The fused ischial rami and diminutive pelvic outlet, coupled with the displaced ossification centers of the distal vertebrae, suggested a relationship between the abnormality being reported and sirenoid monsters. The lower extremities, with the exception of the left clubfoot, were well developed.

The condition of the kidneys was especially interesting. Their alterations were vastly different from the hydronephrosis which usually results from obstruction to urinary outflow. The changes suggested marked chronic inflammation coupled with advanced benign nephrosclerosis. The inflammatory processes resulted in the production of broad constricting and intercepting connective tissue bands. These snared-off groups of tubules were dilated to produce cysts of various sizes and in general distorted the renal architecture. The tubules in places contained débris mixed with green globular material resembling bile. The most plausible explanation of the renal and ureteral changes is that meconium entered the bladder through the tract leading from the bowel. Mixed with urine, it easily passed to the kidneys in retrograde fashion, as the ureters were dilated distally. The bile then acted as an irritant in the tubules and induced an aseptic inflammation which produced the bizarre distortions noted.

12. Hinman, F.: Principle and Practice of Urology, Philadelphia, W. B. Saunders Company, 1935.

SUMMARY

A case of congenital absence of the penis, anus, prostate gland and urethra is reported in a premature infant who had a fistulous tract connecting his atretic large bowel and bladder. The marked inflammatory changes observed in the kidneys are attributed to the irritant effect of bile which entered the urinary system in meconium. The marked pelvic contraction and spinal defects suggest that this body possessed some of the characteristics of sirenoid monsters.

CHRONIC HYPOGLYCEMIA

REPORT OF TWO CASES WITH ISLET ADENOMA AND CHANGES IN THE HYPOPHYSIS

NATHAN B. FRIEDMAN, M.D.
NEW YORK

The syndrome of chronic hypoglycemia associated with islet tumors of the pancreas has become a well recognized clinicopathologic entity because of the striking correlation between the clinical, pathologic and physiologic findings. The review published by Whipple and Frantz [1] summarizes the observations in the earlier cases, and many further reports [2] have appeared, but there are still relatively few containing the results of complete autopsies.

I offer such a study of 2 patients with hypoglycemia who presented several interesting features and clinical problems. Islet adenoma, with islet hyperplasia, marked changes in the pituitary glands and several other lesions of interest were revealed at necropsy. The possible relationship of some of these changes to the hypoglycemia as well as to the obesity which developed in these patients will be discussed.

From the Medical and Laboratory Divisions, Montefiore Hospital for Chronic Disease.

1. Whipple, A. O., and Frantz, V. K.: Ann. Surg. **101**:1299, 1935.

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REPORT OF CASES

CASE 1.—*Summary.*—This patient had suffered from seizures for about two years before the diagnosis of chronic hypoglycemia was made at another institution. He was studied there for one and a half years, and at laparotomy for suspected pancreatic adenoma no tumor was found. He was transferred to this hospital and studied for two years before death occurred during a hypoglycemic attack. Necropsy revealed an islet adenoma of the pancreas and marked adenomatous hyperplasia of the chromophile cells of the pituitary.

History.—A 50 year old Jewish man was admitted to the Montefiore Hospital in June 1935. In October 1933 he had been studied elsewhere for suspected tumor of the brain. At that time he had complained of seizures varying from dizzy spells to episodes of peculiar behavior or even unconsciousness, of which he had been aware for about two years. He was rehospitalized at a second institution in February 1934, after considerable progression of his symptoms. The association of his seizures with low levels of the blood sugar and the relief of symptoms on intravenous administration of dextrose were observed, and the diagnosis of chronic hypoglycemia was established.[3] The presence of extrapyramidal signs, such as parkinsonian facies and gait, loss of associated movements, tremors and slurred, syllabic speech, were considered significant. At laparotomy for suspected islet adenoma of the pancreas, no tumor was found, and biopsies of the liver and pancreas gave essentially negative results.

On examination in June 1935, the markedly obese patient was 160 cm. in height and weighed 92 Kg. An incisional ventral hernia was present. The blood pressure on numerous occasions ranged from 120 systolic and 80 diastolic to 170 systolic and 100 diastolic. The picture suggestive of parkinsonism described was present.

The urine and blood counts were essentially normal. The Wassermann reaction of the blood was negative. The blood sugar was 30 to 60 mg. in 100 cc. (fasting); lactic acid, 15.7 mg.; urea nitrogen, 5 to 12.1 mg.; uric acid, 3.3 mg.; creatinine, 1.8 mg.; cholesterol, 122.9 to 149 mg.; cholesterol esters, 78.8 to 112 mg.; serum albumin, 3.2 to 4.9 mg.; serum globulin, 2.1 to 3.7 mg.; calcium, 10.5 mg.; phosphorus, 3.4 mg.; chlorides, 566 to 604 mg.; carbon dioxide–combining power, 52 to 63 volumes per cent. Sugar tolerance tests showed a rise from low levels to about 150 mg. at one hour with a fall to low levels at two to three hours. Epinephrine (1 cc. of a 1:1,000 solution) caused a rise in blood sugar (60 to 90 mg.) and lactic acid (15.7 to 36.9 mg.) and a fall in phosphorus (3.7 to 2.5 mg.). Insulin caused no more marked fall in the blood sugar than was present spontaneously. It did, however, decrease somewhat the hyperglycemia following administration of dextrose. There was no creatinuria, and the urinary nitrogenous constituents were normal.

Roentgen examination showed a normal sella turcica. The basal metabolic rate (nonfasting) was plus 9 per cent and plus 3 per cent (average calories per hour, 77.8; normal for height and weight, 73.3).

Course.—The previous regimen of a high carbohydrate diet with added feedings was continued. When food was withheld, hypoglycemic symptoms appeared. In mild attacks restlessness, unresponsiveness, sluggishness or sometimes aggressiveness, with paranoid trends, were noted. In more severe attacks the patient became semistuporous, thrashing about with no definite convulsive pattern. During these attacks salivation and diaphoresis were marked, and a positive Babinski sign could

3. Blau, A.; Reider, N., and Bender, M. B.: Ann. Int. Med. **10**:910, 1936.

be obtained. The oral administration of sugar during a mild episode relieved the symptoms in about fifteen minutes, but more severe attacks necessitated administration of dextrose by stomach tube or by intravenous injection. The injection of as little as 1 Gm. of dextrose, with only minimal elevation of the blood sugar, was often striking in its almost immediate restoration of the patient.

During seizures there were no essential changes in the chemical constituents of the blood with the exception of dextrose. The respiratory and pulse rates and the blood pressure rose; extrasystoles or pulsus alternans was occasionally noted, and the skin was mottled and cyanotic. The blood volume (congo red) was unchanged, and there was moderate leukocytosis, but there was no other change in the blood picture.

After prolonged attacks there occasionally occurred spontaneous but temporary improvement with a rise in the blood sugar.

It was found necessary to give the patient a diet of between 50 and 75 Gm. each of protein and fat and of from 700 to 1,000 Gm. of carbohydrate, with frequent feedings, in order to maintain his blood sugar above shock levels. On this regimen his weight rose from 92 Kg. on admission to 130 Kg. at his death, two years later.

Thyroid extract was given on several occasions to the point of toxicity, with a basal metabolic rate of plus 44 per cent (117.9 calories per hour), a treatment which occasionally held his weight level for a few weeks at a time.

With ephedrine, as well as with thyroid extract, the blood sugar levels were slightly higher, but no significant decrease in carbohydrate intake was possible.

The patient complained of increasing weakness, which was not aided by benzedrine, ephedrine and prostigmine, and of difficulty in walking and speaking. He had considerable gastric distress accompanying feedings. Under full atropinization the blood sugar levels were generally lower, although there was considerable alleviation of the difficulty in speaking and walking.

In November 1936 irradiation of the pituitary was tried, the doses totaling 750 roentgens over about a nine day span. Severe exacerbation of the hypoglycemic state followed, so that on a carbohydrate intake on which he had been shock free for some weeks he had frequent severe seizures. The following figures for blood sugar reveal the marked alteration, which was temporary.

	Before Dextrose (30 Gm. Given Orally)	At Given Number of Minutes After Dextrose			
		30	60	90	120
Control	65	130	150	100	55
After irradiation	68	102	47	41	..

Beginning in March 1937, a higher protein diet was given, but the carbohydrate intake could not be reduced significantly. The blood urea nitrogen, however, which had been as low as 5 mg., rose to 12. Protein in the forms of casein (100 Gm.) and meat (400 Gm.) was also substituted for the added carbohydrate in two trials (Conn[4]). The blood sugar level, however, was not maintained, and the onset of hypoglycemic symptoms necessitated the use of carbohydrate.

During 1937 numerous small filiform papillomas appeared on his face, neck and chest. In August 1937 an acute respiratory infection developed, with a rise in temperature to 103 F. During this period it was found possible to cut down his carbohydrate intake considerably and still avoid seizures. This had been noted during a similar episode in December 1935.

On recovery from the infection he had many seizures, and although his carbohydrate intake was increased steadily, the attacks persisted. On the evening

4. Conn, J. W.: J. Clin. Investigation **15**:673, 1936.

of his death he was seen to be restless, and later he lapsed into a typical seizure. On intravenous administration of dextrose he did not respond as usual but became markedly cyanotic and went into collapse, from which he died despite administration of epinephrine.

The conditions finally diagnosed clinically were: chronic hypoglycemia; obesity; encephalopathy of unknown origin; possible islet adenoma of the pancreas.

Pathologic Observations.—The anatomic diagnosis (Dr. David Perla) was: obesity; islet adenoma of the pancreas; basophilic and eosinophilic adenomatous hyperplasia of the anterior lobe of the pituitary; bilateral cortical adenomas of the adrenals; tubular adenoma of the kidney; polypoid adenomas of the ileum; papillomas of the skin; hyperplasia of the interstitial cells of the testis; hypertrophy of the prostate; hyperplasia of the spleen; chronic gastritis; marked congestion and cyanosis of the viscera; cardiac hypertrophy.

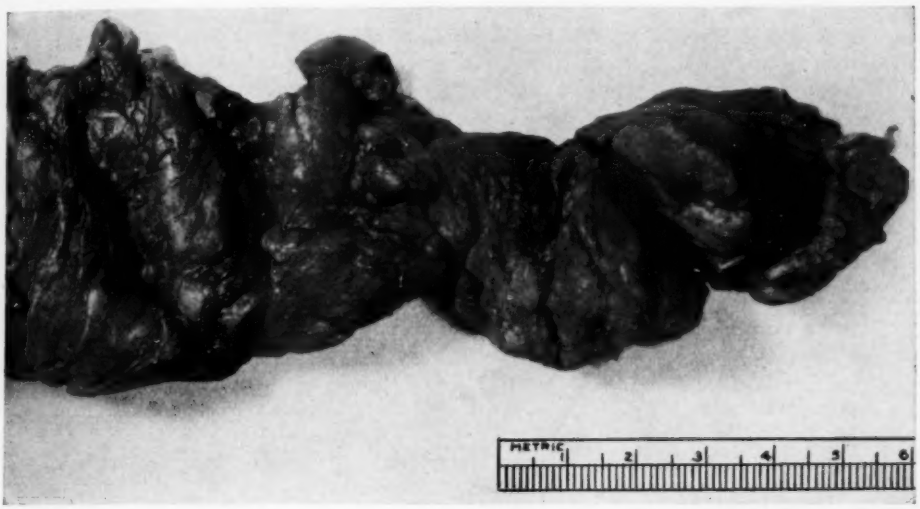

Fig. 1.—Gross appearance of the pancreatic adenoma in case 1.

The body showed extreme generalized obesity. A midline abdominal healed surgical scar, 30 cm. in length, was present. The pupils were dilated, and the face was markedly cyanotic. There were many pedunculated papillomas and fibromas over the face and chest.

All of the viscera showed extreme congestion and cyanosis. The heart weighed 500 Gm. The lungs showed moderate congestion and edema. The 2,500 Gm. liver was intensely congested and cyanotic. The 180 Gm. spleen was grayish red and diffluent. The kidneys together weighed 450 Gm. and were markedly congested. The adrenals together weighed 18.5 Gm., and both showed small cortical adenomas. The thyroid weighed 24 Gm. The seminal vesicles, prostate, bladder and testes appeared normal.

The pancreas weighed 160 Gm. and was very cyanotic and friable. In the tail was a firm nodule, 3 by 2.5 by 2 cm. (fig. 1). It was moderately well encapsulated and showed on section a grayish yellow surface with grayish streaking extending from the capsule.

The brain weighed 1,240 Gm. The right lateral ventricle was narrowed and distorted, and the posterior horn was slightly dilated.

The pituitary weighed 620 mg. On section there were numerous opaque nodules in the anterior lobe. The pineal gland was calcified.

Microscopic Observations.—The heart showed moderate hypertrophy of the muscle fibers. The lungs and liver showed extreme congestion. The kidneys were congested, and a single small tubular adenoma was noted. The adrenals were markedly congested and showed several lipoid-rich cortical nodules. The prostate showed slight adenomatous hyperplasia. The stomach showed thinning of the mucosa and extensive round cell and slight polymorphonuclear infiltration. The testis showed proliferation of the interstitial cells, particularly in one region, where the tubules were atrophic. Spermatogenesis was diminished. The thyroid, parathyroids, spleen and pineal gland showed no essential abnormalities.

The major lesions were in the pancreas and pituitary. The nodule in the pancreas was composed of tissue resembling that of the islets of Langerhans (fig. 2). It showed ribbons and cords of columnar and cuboidal cells, with a thin, delicate stroma of connective tissue and capillaries. In many areas the nuclei, which were oval and vesicular, were basally placed with respect to the capillaries. The fibrous stroma was increased in some portions, and there were isolated nests and clumps of cells. There was a definite fibrous capsule containing similar cell masses. The cytoplasm of the cells was acidophilic and granular.

After fixation in solution of formaldehyde U. S. P. a portion of the adenoma was refixed in a dilute Helly solution and stained with fuchsin orange by the method of Bayley.[5] The cells uniformly showed reddish granules in the cytoplasm. These granules were not as brilliant red as those seen in the beta cells of a section of freshly fixed guinea pig pancreas used as a control. The remainder of the pancreas had undergone such extensive degeneration, presumably post mortem, that histologic studies were out of the question.

The pituitary was fixed in Orth's solution, was sectioned in seven sagittal planes and stained with hematoxylin and with Mallory's connective tissue stain for study (Dr. Charles Spark).

The anterior lobe showed striking hyperplasia of both basophilic and eosinophilic elements with reduction in the number of chromophobes.

The basophilic adenomatous hyperplasia was most marked. There were numerous poorly circumscribed nodules up to 1 mm. in diameter, composed of atypical basophilic cells. These were irregular in size and shape, with large vesicular nuclei, and there were bizarre giant forms and syncytial structures. Transitional forms and cells showing loss of granules were also present in abundance, but vacuoles were scanty and no "colloid" basophils (Crooke[6]) were seen.

Several larger, fairly well circumscribed nodules, up to 4 by 2 mm. in size, with definite compression of capillaries and of the surrounding tissue, were seen (fig. 3). These were composed chiefly of large, fully granulated basophils, although some cells showed pyknotic nuclei and agglutinated granules.

The acidophils were also increased in number, but most of them appeared as broad sheets of normal, fully granulated cells. There was a single 2 by 1 mm. nodule of transitional lightly granulated forms. Near the pars intermedia was an area of large, irregularly shaped cells, only moderately well granulated, but

5. Bayley, J. H.: J. Path. & Bact. **44**:272, 1937.
6. Crooke, A. C.: J. Path. & Bact. **41**:339, 1935.

with huge vesicular nuclei and very prominent nucleoli, resembling cells seen in malignant tumors.

Throughout the anterior lobe there was little follicle formation and no colloid retention. The connective tissue was not increased.

The region of the pars intermedia showed large cysts filled with colloid, and there was moderate infiltration of the pars nervosa with small, irregularly shaped, fairly ripe basophilic cells. However, the degree of infiltration was only a fraction

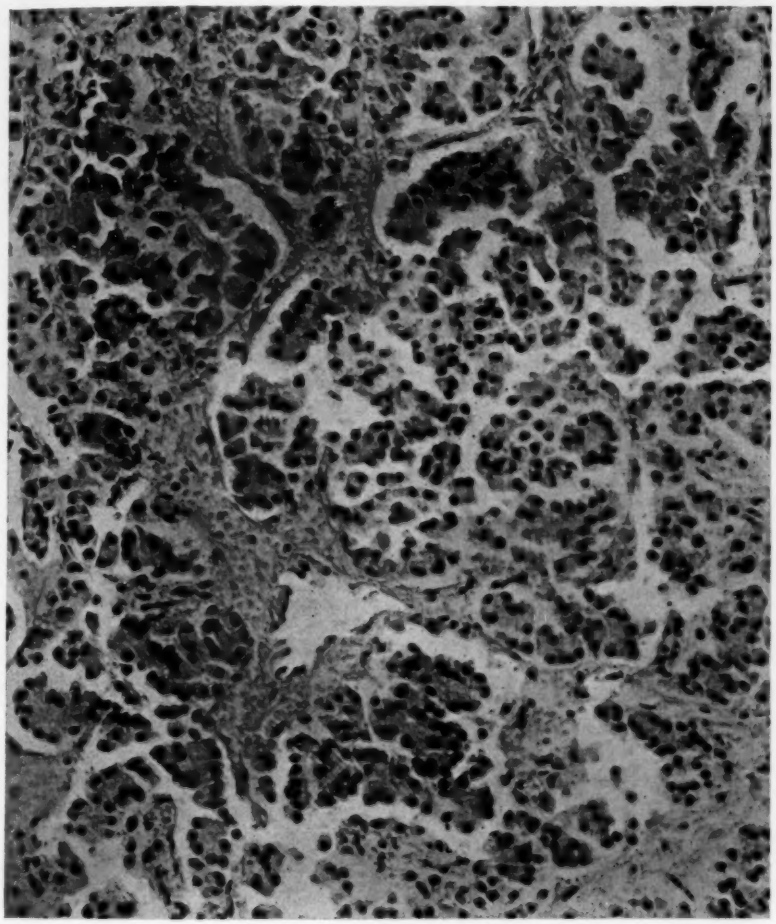

Fig. 2.—Microscopic appearance of the pancreatic adenoma in case 1.

of that seen in the second case. There was no increase in the pigment of the posterior lobe.

A study was made of the brain cortex, basal ganglions, mesencephalon, pons and medulla (Dr. Charles Davison). The vessels were congested, and there were scattered small hemorrhages (agonal). Studies of myelin sheaths showed no abnormalities. In all the regions examined, some of the nerve cells showed the changes of ischemia.

In addition to these changes, some of the cortical nerve cells showed the so-called water changes. In the caudate and putamen occasional nerve cells were disintegrated, and a few Alzheimer glia cells (types 1 and 2) were noted. There was marked calcification of some of the pallidal blood vessels. There was an occasional water cell in the thalamus.

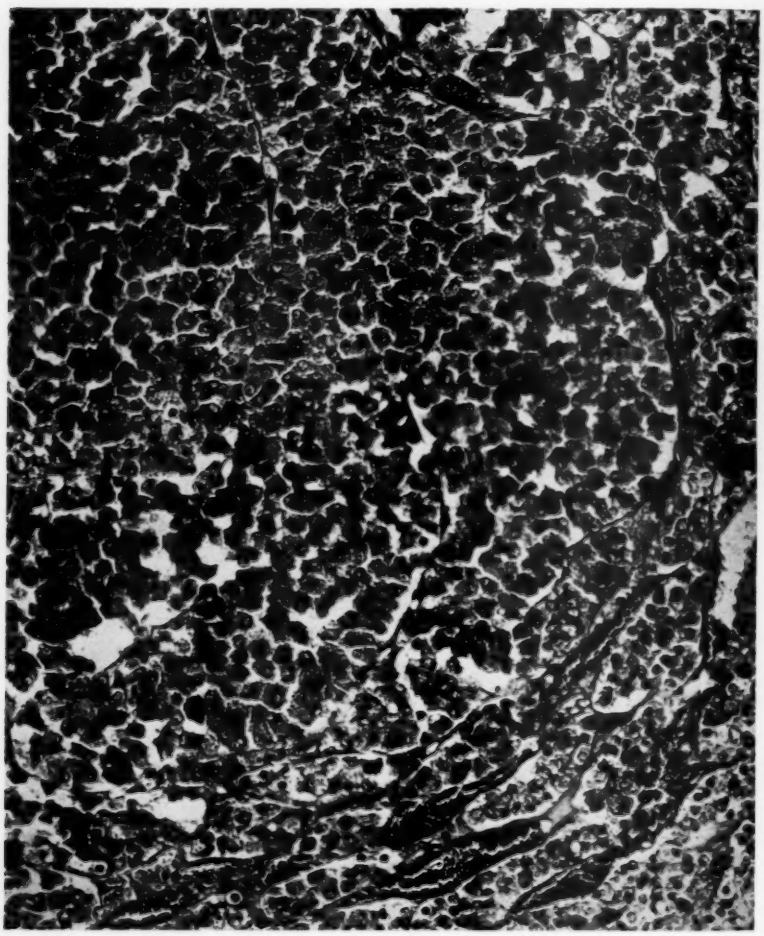

Fig. 3.—A nodule in the pituitary in case 1.

The cells of the nucleus supraopticus, nucleus paraventricularis, nucleus reuniens, nucleus mamilloinfundibularis and nuclei tuberis showed poverty of the usual pigmentary deposits, and in the nucleus basalis such deposits were absent. There were a few vacuolated cells in one area of the nucleus paraventricularis.

Case 2.—*Summary.*—The patient had suffered from seizures for three years, which were associated with a low level of the blood sugar and could be relieved by the administration of sugar. Focal neurologic signs were present. When

increased intracranial pressure became evident, study suggested a tumor of the left side of the brain. Craniotomy revealed a large subdural hematoma, which was removed, but the patient died eighteen days after the operation. Necropsy revealed an islet adenoma of the pancreas, marked hypertrophy and hyperplasia of some of the islets of the pancreas, marked adenomatous hyperplasia of the chromophile cells of the pituitary and a fungus infection of the esophagus.

History.—A 56 year old Jewish man was admitted to the Montefiore Hospital in January 1936. He gave a history of occasional attacks of dizziness over a period of three years, associated with stiffness and loss of control of the right arm and leg during seizures. In the year preceding admission he had seizures while asleep, during which he mumbled and shouted, thrashed about with his right arm and leg, became flushed and perspired, and from which he could not be aroused. The attacks increased in frequency and were relieved or prevented by the taking of food or orange juice. Increasing hunger was noted, and the patient had gained about 25 pounds (11.3 Kg.) in weight in six months. During one attack in September 1935 he had fallen down a flight of stairs.

Examination showed an obese man, weighing 74 Kg. and measuring 160 cm. in height. The blood pressure was 130 systolic and 90 diastolic. There were tortuous peripheral vessels and slight retinal arteriosclerosis. There was very slight right hemiparesis.

The urine and blood counts were normal. The Wassermann test of the blood was negative. The blood sugar was 45 to 59 mg. in 100 cc. (fasting); lactic acid, 16.3 mg.; urea nitrogen, 16.8 mg.; calcium, 12.2 mg.; phosphorus, 4.8 mg.; chlorides, 597 mg.; serum albumin, 4.7 mg.; serum globulin, 3.2 mg.; cholesterol, 122 mg. Sugar tolerance tests revealed a basal level of 50 mg. or lower and a peak of over 100 mg. at one hour and a fall to low levels at three hours. Epinephrine caused a rise in blood sugar (56 to 95 mg.) and lactic acid (16.3 to 40.5 mg.). Insulin did not recognizably accelerate the spontaneous fall in blood sugar but decreased the hyperglycemia induced by dextrose.

Shortly after admission the patient was seen in an attack, during which he became noisy and nonresponsive. He sweated, flushed and had occasional twitchings of the mouth and hands. Such seizures could be produced by fasting and were associated with low levels of the blood sugar. Dextrose given by mouth relieved attacks in from ten to fifteen minutes, and dextrose injected by vein was almost immediately active, even in small amounts (less than 5 Gm.).

The patient was placed on a diet high in carbohydrate (370 Gm.), with frequent added feedings to maintain the blood sugar above shock levels.

In April 1936 nausea and vomiting gradually developed, with frontoparietal headache on the left side.

The essential observations were those of right hemiparesis, which had not progressed from that noted on admission and which had been considered the residuum of an old unnoticed cerebral vascular accident. The fundi revealed hyperemic disks with blurred margins and engorged veins, although there was no measurable elevation.

Lumbar puncture disclosed a spinal fluid pressure of 260 mm. of water. The fluid was normal. The temperature at about this time had risen occasionally and irregularly to 102 F. without obvious cause. The patient had become partially disoriented, facetious and euphoric. Encephalography revealed the left lateral ventricle to be larger than the right and displaced beyond the midline. The right lateral ventricle was partly filled and was displaced to the right and downward. The third ventricle was dilated and displaced to the right.

On April 29 a left frontoparietal craniotomy was performed by Dr. Ira Cohen, the temperature having fallen to normal preoperatively. A huge subdural hematoma was disclosed extending over practically the whole left hemisphere and beneath the temporal and frontal poles. It was up to 3 cm. in thickness and was partially liquefied, containing 50 cc. of dark brown material. The entire hematoma, which was somewhat adherent to the dura, but practically not at all to the arachnoid, was removed in pieces.

Postoperatively there was no change in the hypoglycemic state, and the blood sugar was maintained above shock levels on the same regimen as was described.

At first the patient's general condition was good, but on the eleventh postoperative day his temperature began to rise, and he became semistuporous, with Cheyne-Stokes respiration, and had intractable hiccup, abdominal distention and incontinence. When a series of convulsions involving the left arm and the right leg appeared, a postoperative hematoma was suspected, but bilateral frontoparietal bore holes revealed none. On May 16, with a blood pressure of 80 systolic and 55 diastolic, pulmonary edema developed and the patient died, with a terminal temperature of 104 F. The blood sugar on the last two days had risen to 280 and 320 mg. on the forced carbohydrate regimen, but there was no acetonuria.

The conditions finally diagnosed clinically were: chronic hypoglycemia; obesity; status after craniotomy for subdural hematoma; possible islet adenoma of the pancreas.

Pathologic Observations.—The anatomic diagnosis (Dr. Henry Brody) was: obesity; hyperplasia of the islets of Langerhans with the formation of single large islet adenoma; basophilic and eosinophilic adenomatous hyperplasia of the anterior lobe and basophilic infiltration of the posterior lobe of the pituitary; craniotomy; extradural hematoma; bronchopneumonia of the left lower pulmonary lobe; fibromyoma of the esophagus; pseudomembranous (fungous) esophagitis.

The body showed marked generalized obesity, and there was a great abundance of fat in the usual depots. There was a partially healed semicircular scalp incision in the left frontoparietal region, with a loose underlying bone flap. There was a second short incision over the right frontoparietal area, with a small bone defect underneath.

The heart weighed 400 Gm., and there was moderate atherosclerosis of the coronary arteries. The lungs were congested, and the left lower lobe showed small patches of bronchopneumonia with fibrinous pleuritis. The esophagus was adherent to the adjacent structures and showed marked wrinkling and thickening of the brownish mucosa. At the junction of the esophagus with the stomach was a fibromyoma, 2 by 1 cm. The stomach was dilated. The liver (2,500 Gm.), the spleen (210 Gm.) and the kidneys (370 Gm. together) appeared normal.

The pancreas was normal in size and shape and showed a moderate interlobular infiltrate of fat. At the junction of the body and head, at the upper edge of the posterior surface, was a firm spherical 1 cm.-sized encapsulated nodule, fairly well demarcated from the surrounding pancreatic tissue. It cut with increased resistance, showing a chalky white surface with a few 1 mm.-sized purplish areas.

Under the left frontoparietal bone flap there was a fairly large organized extradural hematoma. The 1,700 Gm. brain was flattened in the region of the flap, was generally congested and was slightly indented over the right orbital convolutions. On section the left ventricle was constricted, while the third ventricle was distorted and shifted to the right.

The pituitary weighed 660 mg. On sagittal section opaque whitish tissue replaced most of the normally glistening and translucent posterior lobe. The anterior lobe showed numerous small whitish opaque nodules.

The pineal gland appeared normal. The thyroid, parathyroids and testes were not examined.

Microscopic Observations.—The liver showed a few small foci of fatty change and slight central congestion.

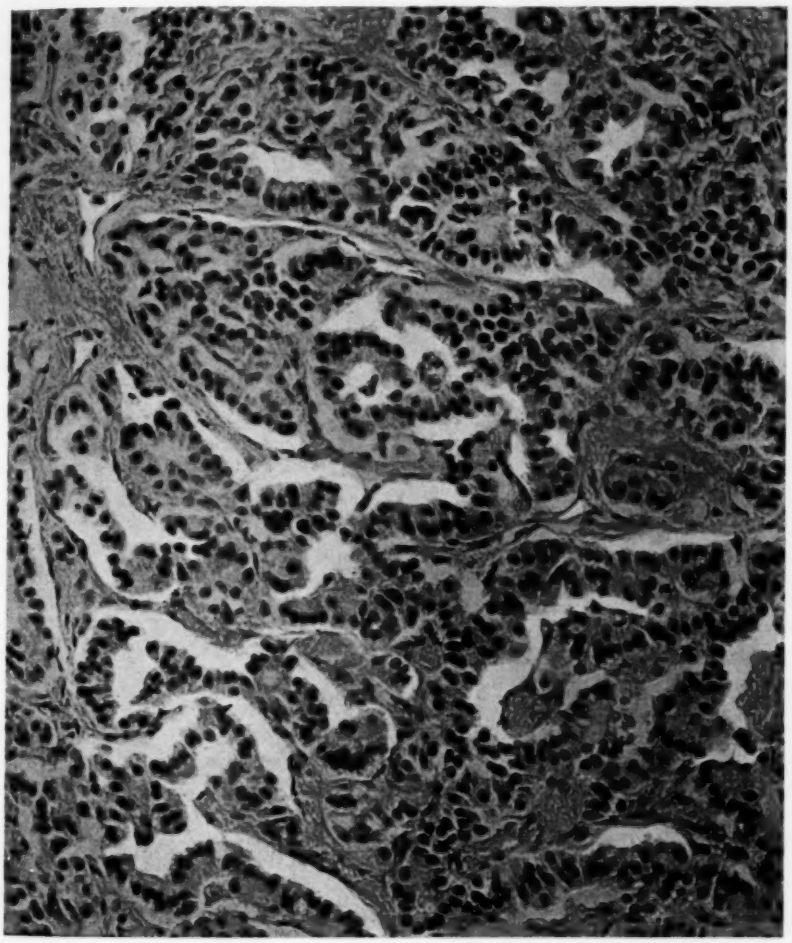

Fig. 4.—Microscopic appearance of the pancreatic adenoma in case 2.

There was a tiny infarct of the spleen, but the heart, lungs, kidneys, adrenals, prostate and pineal gland showed no essential abnormalities.

The major lesions were found in the pancreas, pituitary and esophagus. The nodule in the pancreas suggested an islet adenoma. It was composed of ribbon-like cords of columnar cells with a pale granular cytoplasm and regularly arranged oval nuclei (fig. 4). The cords were frequently one cell layer thick, with delicate

stroma and capillaries on both sides. In some places, double layers and papillary structures were present. In others there were glandular structures with basally placed nuclei. Solid masses of cells were present in some areas. The resemblance to islet tissue was definite. In some regions the cells showed pyknosis of the nuclei and disappearance of the cellular outline, with pale myxomatous, hyalin-like material deposited interstitially and perivascularly. Slight to severe fibrosis was present throughout, with fibrous septums transversing the adenoma. These were continuous with a thick fibrous capsule in which both adenomatous tissue and pancreatic acinar tissue were present. Ductlike structures were present in the adenoma and the capsule and at points along the capsule strongly suggested continuity with the adenomatous tissue, although serial sections failed to demonstrate this definitely. In one of these areas a few bizarrely shaped hyperchromatic nuclei and multinucleated cells were seen.

The pancreas elsewhere showed areas of fibrosis and fatty infiltration. The acinar tissue was not remarkable, but there were definite changes in the islets. Most of the islets appeared normal, but in a few areas in the head, near the adenoma, they were unusually large and numerous and showed a cellular structure unlike that of the other islets. They were composed of ribbons and cords of columnar cells and markedly resembled the tissue seen in the adenoma (fig. 5).

The pancreas, at first fixed in Jores [6a] solution, was refixed and stained as in case 1. Although the preparations were not completely satisfactory, the normal-appearing islets showed both pale cells and cells with reddish granules in their cytoplasm. The former were considered to be of the alpha and the latter of the beta type. The cells of the adenoma uniformly showed a reddish granular cytoplasm similar to that seen in the beta cells.

The pituitary gland was fixed and stained as in case 1 and studied in five sagittal planes (Dr. Spark). The anterior lobe showed adenomatous hyperplasia of both the basophilic and the acidophilic cells, preponderantly the former. The chromophobe cells were reduced in number. Throughout the anterior portion were numerous large and small masses of basophilic cells in all stages of evolution. Some contained deeply stained granules; others were of the transitional type, with granules that stained light grayish blue. The cells were irregular in shape and size, and the nuclei tended to be large and vesicular. Binucleated basophilic cells were not uncommon, and vacuoles were large and numerous. No "colloid" basophils were found.

On the inferior surface of the anterior pole near the midline was a 4 by 1 mm. fibrosing basophilic adenoma, consisting of irregularly shaped nests of transitional basophils, separated by a moderate amount of loose stroma. At the same level were large groups of transitional basophilic cells undergoing necrobiosis, with small pyknotic nuclei, poorly defined cell membranes and marked loss of granules. At another level was a fairly well circumscribed mass, 1 mm. in diameter, of deeply granulated basophils with a few degenerated forms. In the posterior half of the anterior lobe the acidophils formed broad sheets of deeply granulated cells with only an occasional included basophil. The cells were typical, with normal nuclei, and showed little variation in size and shape. On the inferior surface near the anterior tip was a small oval adenoma composed of transitional acidophils and a few ripe basophilic elements.

There was relatively little follicle formation in the anterior lobe, and the connective tissue stroma was increased in a few areas.

6a. Mallory, F. B.: Pathological Technique, Philadelphia, W. B. Saunders Company, 1938.

The region of the pars intermedia contained a few moderate-sized cysts filled with colloid.

The posterior lobe showed a striking picture of massive infiltration by closely packed ripe basophil cells. These cells resembled the basophils of the anterior lobe in all respects except that only a few transitional forms were present, and

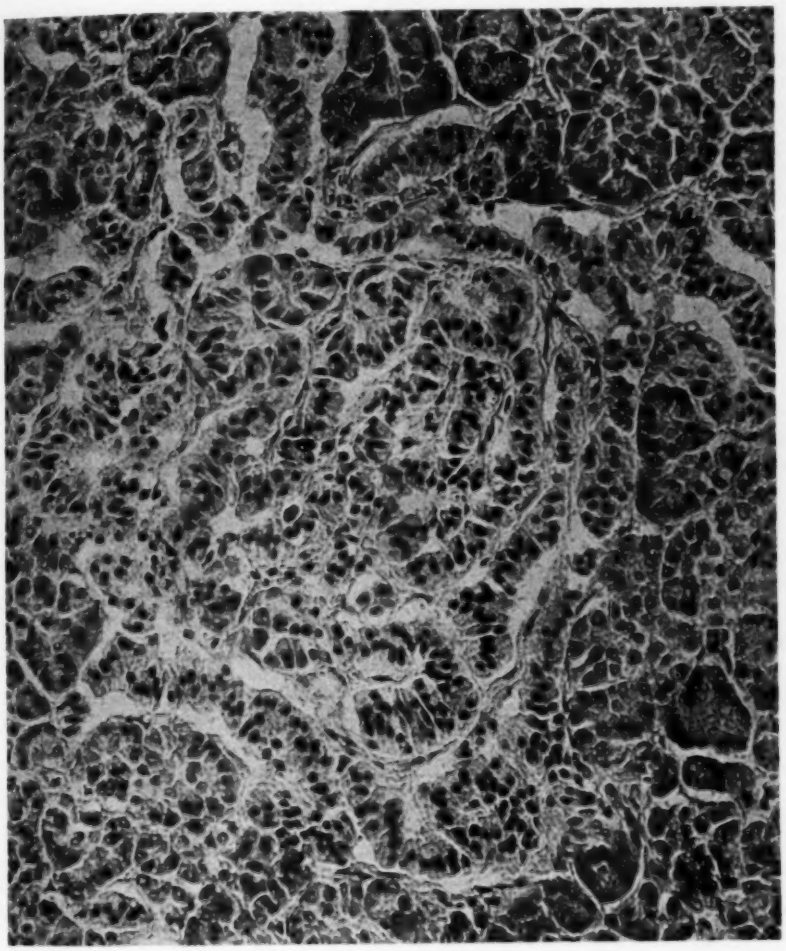

Fig. 5.—Microscopic appearance of a hyperplastic islet in the pancreas in case 2.

there was some follicle formation and colloid retention. From one half to three quarters of the pars nervosa was occupied by these basophilic elements (fig. 6). In some areas the capsule over the posterior lobe was also invaded by basophils. There was a moderate amount of pigment in the uninvaded portion.

The esophagus showed an extensive necrotic exudate replacing the mucosa and extending deeply into the muscle layers. There was edema, with considerable infiltration by inflammatory cells, chiefly lymphocytes, plasma cells and macrophages,

and a few polymorphonuclear leukocytes. Miscellaneous bacteria were present in the Gram preparation, with numerous larger forms showing branching hyphae and spores infiltrating the inflammatory membrane in palisade fashion, suggesting a fungus infection.

The cortical and hypothalamic regions of the brain were studied (Dr. Davison). The arterioles of the cortex showed proliferation of the endothelium, and the nerve cells showed the changes of ischemia. The nerve cells of the hypothalamic nuclei showed some poverty of iron pigment, while those of the paraventricular and supraoptic nuclei were swollen as well. The nerve cells of the nuclei tuberis proper were normal.

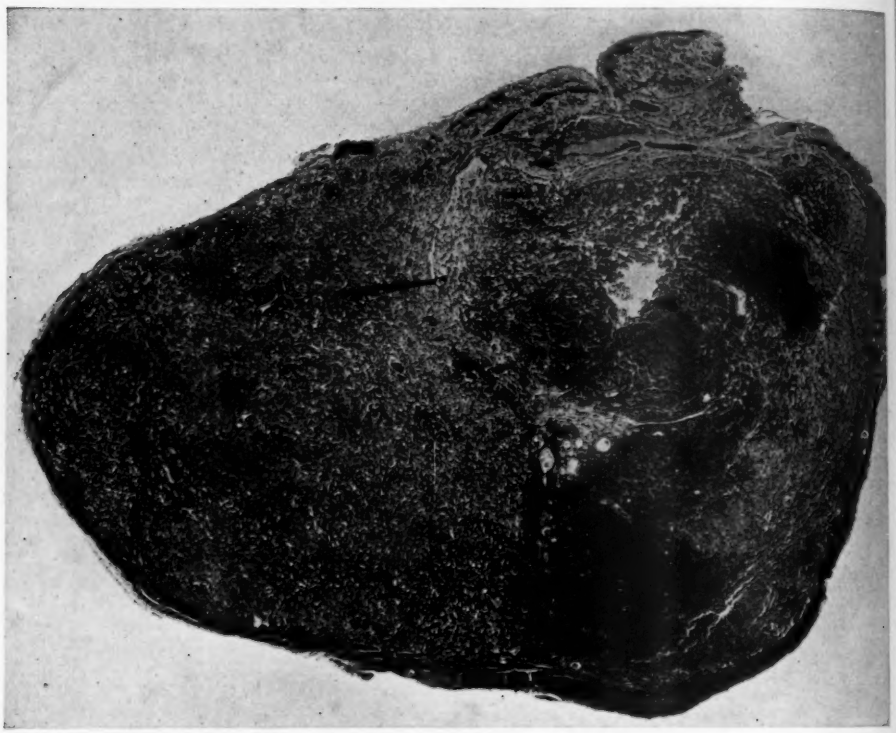

Fig. 6.—Microscopic appearance of the pituitary in case 2. Note the infiltration of the posterior lobe.

COMMENT

Clinical Observations.—One feature of interest was the dural hematoma confusing the clinical picture in case 2. This hematoma had been sustained, presumably, as a result of trauma during an earlier seizure. The possibility of such a complication in cases of this type should be borne in mind. In a case of Reiter's [2m] previous injury of the skull and the presence of focal neurologic signs were similarly misleading. The failure of operative exploration to disclose a pancreatic adenoma as in case 1 has been reported. In this case, too, there was evidence of a disease of the central nervous system.

The effect of infection in temporarily ameliorating the severity of the hypoglycemic state in case 1 corroborates the observations of Blau, Reider and Bender [3] on the same patient. They had observed, in addition, that the administration of typhoid vaccine, with fever, had a similar effect.

The opposite result, marked exacerbation of the hypoglycemia following irradiation of the pituitary region, is interesting in view of the well known effects of hypophysectomy on sensitivity to insulin.

One of the most significant of all the changes noted in chronic hypoglycemic patients of this type, one that has been commented on by many observers, is the marked progressive obesity. This was present in both of our cases and may be due to the high caloric diets given therapeutically or taken spontaneously by such patients. It is tempting to speculate on this phenomenon as a clue in unraveling the genesis of some types of obesity. Falta many years ago suggested that obesity may be related to overactivity of the pancreas, and in this type of case such a possibility has become an actuality. This might be considered a true endocrinal form of obesity with a definite anatomic and physiologic basis in the islet tumor and the hypoglycemia.

Among others, Massa,[7] Kup,[8] Harris [9] and Lichtwitz [10] have in recent years discussed this relationship. Ogilvie [11] found more islet tissue than in the controls in the pancreas of the obese subject and hypoglycemic sugar tolerance curves in one third of his cases of early obesity. The finding of increased sugar tolerance in obesity has again been reported by Leites and Agaletzkaja.[12] Insulin has been used therapeutically to increase weight for some time, although there have been some contradictory studies. Mackay and Callaway [13] recently produced obesity in animals by the use of protamine insulin, and I have confirmed this observation.[14]

Pathologic Observations.—The adenomas in the pancreas were quite typical. The histologic characters of such tumors have been studied in detail by O'Leary and Womack [15] and by Laidlaw.[16] The ribbon-

7. Massa, M.: Gior. di clin. med. **10**:679, 1929.
8. Kup, J.: Endokrinologie **6**:102, 1930.
9. Harris, S.: Am. J. Digest. Dis. & Nutrition **2**:557, 1935.
10. Lichtwitz, L.: Pathologie der Funktionen und Regulationen, Leiden, A. W. Sijthoff's Uitgeversmaatschappij N. V., 1936.
11. (*a*) Ogilvie, R. F.: J. Path. & Bact. **37**:473, 1933. (*b*) Ogilvie, R. F.: Quart. J. Med. **4**:345, 1935.
12. Leites, S., and Agaletzkaja, A.: Acta med. Scandinav. **89**:199, 1936.
13. Mackay, E. M., and Callaway, J. W.: Proc. Soc. Exper. Biol. & Med. **36**:406, 1937.
14. Unpublished data.
15. O'Leary, J. L., and Womack, N.: Arch. Path. **17**:291, 1934.
16. Laidlaw, F. G.: Am. J. Path. **14**:125, 1938.

like cords of cells resembling those described by MacCallum [17] and Cecil [18] in islet hypertrophy are interesting particularly in view of the changes found in the other islets in case 2. Many of the islets near the adenoma revealed a histologic picture quite like that of the adenoma itself, and exhibited these ribbons. This change suggests a more diffuse islet hyperplasia with adenoma formation rather than the occurrence of a single localized tumor. It is unfortunate that in case 1 the pancreas was not sufficiently well preserved for studies of the islets throughout the organ. Several observers have noted that in cases of hypoglycemia with islet adenoma the pancreatic islets show such changes. Cases in which multiple adenoma or even diffuse adenomatosis was present have been reported. Specific granules were demonstrated in the cells of both adenomas. As other studies have shown, the granules resembled beta granules, although they were not quite typical.

The changes in the pituitary gland were marked. The massive basophil infiltration of the posterior lobe in the one case and the relatively slight infiltration in the other are possibly of less significance than the marked adenomatous hyperplasia in the anterior lobe.

Similar changes have been described in other cases of islet adenoma with hypoglycemia. Terbrüggen's [19] case showed two "chief" cell adenomas. In the case reported by Rienhoff and Lewis [20] an excess of basophils was observed and two tiny adenomas without specific granules but "staining more deeply with ordinary stains." There was also basophilic infiltration of the posterior lobe. In the case reported by Malamud and Grosh [21] eosinophilic hyperplasia and a small basophil adenoma were noted.

Another type of change, which is considerably more complex, has been seen in 2 cases. In a case studied by Kalbfleisch [2n] there were multiple pancreatic adenomas. One of these had been surgically removed because of progressing hypoglycemia in spite of the presence of a Fröhlich syndrome complex and roentgen evidence of damage to the sella turcica. At necropsy the other islet tumors were found. There was a chromophobe adenoma of the pituitary extending out of the sella. The compressed pituitary showed slight basophil infiltration of the posterior lobe, and in the anterior lobe the eosinophils were more numerous than the basophils and the latter more numerous than the chromophobes. The parathyroids showed changes suggesting chief cell adenoma, and softness of the bones was noted. This case is reminiscent of the one

17. MacCallum, W. G.: Am. J. M. Sc. **133**:432, 1907.
18. Cecil, R. L.: J. Exper. Med. **13**:595, 1911.
19. Terbrüggen, A.: Beitr. z. path. Anat. u. z. allg. Path. **88**:37, 1932.
20. Rienhoff, W. F., Jr., and Lewis, D.: Bull. Johns Hopkins Hosp. **54**:386, 1934.

reported by Lloyd,[21] in which the pituitary tumor dominated the clinical picture. A 22 year old obese woman with male distribution of hair and hypogenitalism died after operation. She showed glycosuria once. At necropsy multiple nodules composed of islet tissue and many large islets were found in the pancreas. There was an extrasellar chromophobe adenoma of the pituitary. The gland was reported as otherwise normal. The parathyroids were large and showed chief cell adenomas.

The pituitary changes in the 3 cases first mentioned and in the 2 cases reported in this paper certainly indicate active disease of some sort, but their exact significance must await further study. It is once more tempting to consider these changes as possibly related to the changes found in the pituitary in cases of obesity. Zeynek [22] and Muller,[23] among others, found an increase in the number of basophils in the pituitary and the formation of basophil and transitional cell adenomas in persons suffering from obesity to a greater extent than in nonobese persons. Spark [24] in his laboratory confirmed these observations (unpublished).

Changes in the central nervous system have occupied the attention of many workers. Various degenerative processes have been described by Terbrüggen,[19] Baker and Lufkin,[25] Moersch and Kernohan,[26] Malamud and Grosh [21] and many others. Experimental hyperinsulinism and the changes in the central nervous system have also been investigated, a recent report being that of Weil, Liebert and Heilbrunn.[27] In the cases reported in this paper the changes found were consistent with their observations.

Multiple adenomas in many endocrine glands and viscera, such as have been found in some of the reported cases and in my case 1, have been taken by Lichtwitz [10] and others to indicate that a central neurohumoral mechanism of some sort may be primarily at fault. In the presence of lesions in the central nervous system, such a possibility deserves consideration.

In my case 1, in which death occurred while the patient was in hypoglycemic shock, the intense cyanotic congestion of the viscera resembled that reported in a case of Ziskind's. The esophagitis and

21. Lloyd, P. C.: Bull. Johns Hopkins Hosp. **45**:1, 1929.

22. Zeynek, E.: Frankfurt. Ztschr. f. Path. **44**:387, 1933.

23. Muller, M.: Endokrinologie **18**:114, 1936.

24. Spark, C.: Unpublished data.

25. Baker, A. B., and Lufkin, N. H.: Arch. Path. **23**:190, 1937.

26. Moersch, F. P., and Kernohan, J. W.: Arch. Neurol. & Psychiat. **39**:242, 1938.

27. Weil, A.; Liebert, E., and Heilbrunn, G.: Arch. Neurol. & Psychiat. **39**: 467, 1938.

gastritis as possible complications of the hypoglycemia and the intake of large amounts of carbohydrate are somewhat interesting.

SUMMARY

Two cases of chronic hypoglycemia, in each of which an islet adenoma of the pancreas was found at necropsy, are reported. In both cases marked hyperplasia of the basophilic and eosinophilic cells of the pituitary was noted. In one case hyperplastic changes in the islets of Langerhans suggested that the adenoma might be related to a generalized change in the islet apparatus.

The significance of the changes in the pancreas and pituitary are discussed with particular reference to the obesity that developed in both patients.

OBSERVATIONS ON LESIONS PRODUCED IN ARTERIES OF DOGS BY INJECTION OF LIPIDS

LIPIDS INJECTED: HUMAN FAT, FATTY ACIDS, SOAPS AND CHOLESTEROL

OSCAR O. CHRISTIANSON, M.D.
UNIVERSITY, ALA.

Focal lesions of arteries have been produced experimentally in several ways. Schilling [1] produced such lesions in the arteries of rabbits by searing and tearing the walls and by stripping off the adventitia. Ssolowjew produced them by stretching [2] and cauterizing [3] the arteries. Anitschkow [4] and Ssolowjew traumatized arteries of rabbits fed a high cholesterol diet in order that they might determine the effect of mechanical injuries on the deposition of lipids.

There apparently has been no investigation of the effects produced in the walls of arteries by injections of various known lipids. Studies have been made, however, of lesions produced in other tissues by injections of fat materials. Wail [5] injected lipids into the subcutaneous tissues of rabbits and by microchemical studies followed the changes in the composition of the fats as well as the tissue reactions at intervals after the injections. Hirsch [6] studied lesions occurring in the lungs of rabbits after several intravenous injections of lipids. Hagerty [7] produced lesions in the kidneys of rabbits and dogs, similar to those seen in diffuse glomerulonephritis, by injecting lipids into the renal arteries.

The tissue lesions which I have studied were produced by injecting lipids into arterial walls in dogs. These lipids consisted of human fat alone or human fat mixed with one or more of the following ingredients: oleic acid, stearic acid, cholesterol or these acids neutralized with

From the John Jay Borland Fellowship for Clinical Research of the Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago, and the Department of Pathology of the University of Alabama Medical School, University, Ala.

1. Schilling: Verhandl. d. deutsch. path. Gesellsch. **20**:154, 1925.
2. Ssolowjew, A.: Ztschr. f. d. ges. exper. Med. **69**:94, 1930.
3. Ssolowjew, A.: Virchows Arch. f. path. Anat. **283**:213, 1932.
4. Anitschkow, N.: Beitr. z. path. Anat. u. z. allg. Path. **59**:306, 1914.
5. Wail, S. S.: Virchows Arch. f. path. Anat. **245**:219, 1923.
6. Hirsch, E. F.: (*a*) Arch. Path. **21**:765, 1936; (*b*) **25**:35, 1938.
7. Hagerty, C. S.: Arch. Path. **25**:24, 1938.

aqueous solutions of sodium hydroxide or calcium hydroxide. A comparative study was made of the tissue reactions induced, at various intervals of time.

MATERIALS AND METHODS

Sterile solutions of the lipids were injected into the media and subintimal tissues of the abdominal aorta and femoral arteries through a 26 gage hypodermic needle. Frequently the lumen of the vessel was entered by the needle and a small hemorrhage resulted. In control experiments to determine the tissue reactions induced by the extravasated blood, the arteries were pierced several times. Eighty dogs, anesthetized with pentobarbital sodium for the operation, were killed with ether. The arterial segments were fixed in solution of formaldehyde U. S. P. (1:10) and in Zenker's solution. Those fixed in the formaldehyde solution were sectioned by the freezing method, stained with scarlet red and counterstained with hematoxylin. Sections were mounted unstained and examined with a micropolariscope for cholesterol esters. Sections from each vessel were examined by the Schultz[8] method to detect minute quantities of cholesterol. Tissues fixed in Zenker's solution were embedded in paraffin, cut, and stained with hematoxylin and eosin and with phosphotungstic acid–hematoxylin.

MICROSCOPIC OBSERVATIONS AT SITES OF INJECTION OF TEST SUBSTANCES

Human Fat.—At the end of the first day the region about the fat in the media and adventitia was infiltrated by many polymorphonuclear leukocytes. Usually there were marked fatty changes of the surrounding muscle fibers. The internal elastic lamina was slightly swollen. The capillaries of the media were dilated. The intimal lining cells were swollen and partly desquamated. In five days a vascular and edematous granulation tissue had formed. In this were masses of large mononuclear cells, many containing fine fat globules. The cellular reaction was most marked at the end of the first week. The lesion consisted mainly of chronic exudate cells, a few fibroblasts and an occasional polymorphonuclear leukocyte. The reaction was more marked in the adventitia than in the media. When fat was injected into the media, an intimal plaque usually formed within five to seven days. Most of these plaques were directly continuous through a destroyed portion of the internal elastic lamina into the fibroblastic tissues about the fat in the media. The new plaques consisted of many oval and round cells that seemed to proliferate locally. In the older lesions the cells were spindle shaped and separated by abundant collagenous fibers.

After twenty-eight days most of the fat was absorbed from the media. The remaining fat was surrounded by a fibroblastic tissue with many mononuclear cells. The lipid contained a greater proportion of crystalline fat than at the time of injection. In eight to ten weeks the crystals and granular fat débris often lay free in close proximity to large mononuclear cells. In other places they were surrounded by dense acellular scar tissue. Some of the old medial scars were scarcely visible; the internal elastic lamina remained interrupted, but there was often reduplication or splitting near its broken ends. In two hundred and twelve days the changes were similar except that only traces of fat remained, and the scars were smaller.

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8. Schmorl, G.: Die pathologisch-histologischen Untersuchungsmethoden, ed. 16, Berlin, F. C. W. Vogel, 1934, p. 180.

Human Fat Neutralized Over an Aqueous Solution of Sodium Hydroxide.—The lesions resembled those caused by non-neutralized fat (fig. 1 *A*). The rate of absorption of the fat appeared slightly more rapid after neutralization.

Human Fat with 5 Per Cent Cholesterol.—This is approximately a saturated solution at 37.5 C. The acute inflammatory changes in the first few days were like those caused by fat alone, but after the first week the granulation tissue was more extensive and cellular. Many foreign body giant cells and clusters of large mononuclear cells were about acicular cholesterol crystals or fat droplets. The healing process was slow. Even after ten weeks some arteries had a considerable infiltrate of large mononuclear cells and foreign body giant cells about an occasional cholesterol crystal. No foreign body giant cells were noted in the media. In a healed lesion of one artery were two long acicular cholesterol crystals embedded in a small dense scar of the media just below the intact internal elastic lamina. At this level there was also a small intimal fibrous plaque. The scars were slightly larger and denser than those induced by human fat.

Human Fat with 16 Per Cent Oleic Acid.[9]—In the first few days slight necrosis and hemorrhage appeared about the lipid. In five to fourteen days the lesions were like those produced by human fat combined with cholesterol except that the foreign body giant cells were not so numerous (fig. 1 *B*). The fat was absorbed rapidly, and after twenty-eight days most of the arteries contained only traces of fat globules, a few fat crystals and granular débris. Although the initial tissue reaction was marked, a healed lesion resulted considerably sooner than after the injection of fat alone or combined with cholesterol.

Human Fat, 16 Per Cent Oleic Acid and 5 Per Cent Cholesterol.—This was not a saturated solution of cholesterol at 37.5 C. All lesions were observed one hundred and fifty-five to one hundred and seventy-eight days after the injection. There were small scars with occasional large mononuclear cells. In one artery a cluster of small acicular cholesterol crystals was embedded in a dense acellular scar of the adventitia.

Human Fat and 16 Per Cent Oleic Acid Neutralized Over an Aqueous Solution of Calcium Hydroxide.—The tissue response in the first two to three weeks was similar to that induced by mixtures of human fat and oleic acid. Many foreign body giant cells and mononuclear cells were about small free-lying granules of calcium oleate. The lipids, however, were absorbed more slowly, and the lesions were more chronic than those caused by the aforementioned solution (fig. 2 *A*).

Human Fat and 16 Per Cent Stearic Acid.—In one artery examined one hundred and eighty-four days after the injection of the fat a small scar of the media remained. Overlying this was a small intimal plaque of swollen and granular collagenous fibers (fig. 2 *B*).

Human Fat, 16 Per Cent Oleic Acid and 5 Per Cent Cholesterol Neutralized Over an Aqueous Solution of Calcium Hydroxide.—These arteries were examined thirty-seven days and one hundred and forty-eight days after the injection. The tissue response resembled the others. In the older lesion a small cluster of cholesterol crystals was in a scar of the adventitia.

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9. The oleic acid was prepared by P. J. Hartsuch in the Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago. This purified acid had an iodine number of 99.4 and an acid number of 198.4. The percentage of oleic acid was approximately 92 and of linoleic acid 8.

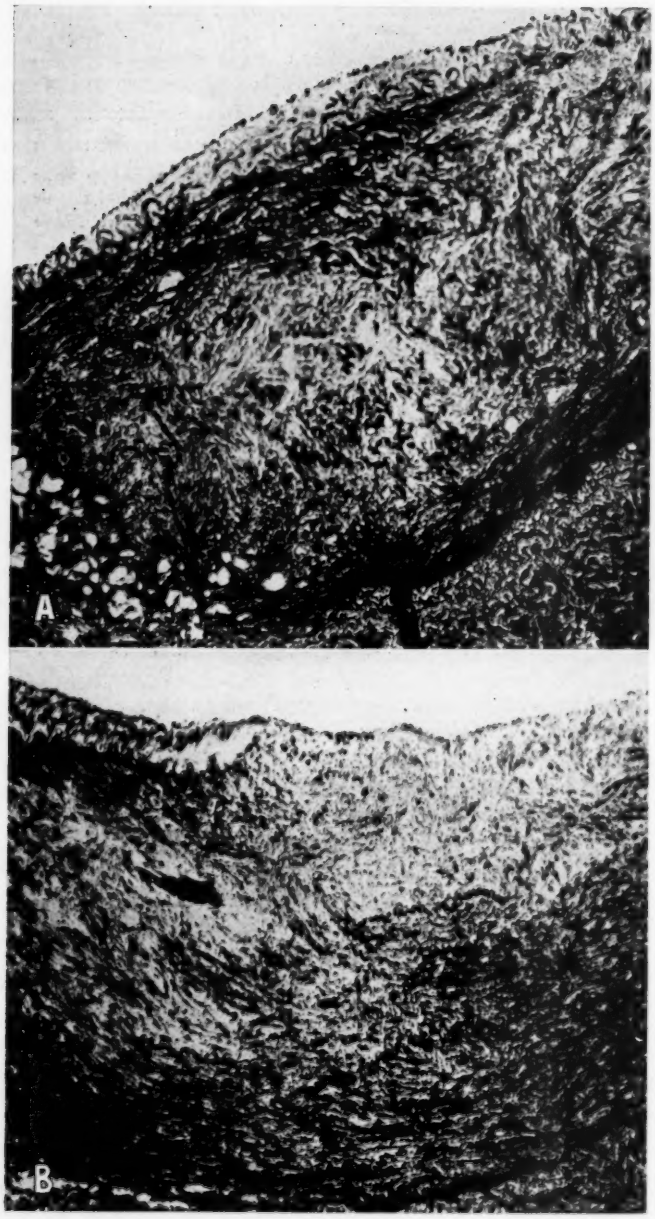

Fig 1.—*A*, photomicrograph of the femoral artery of a dog thirteen days after human fat neutralized by sodium hydroxide had been injected into the media; × 124. Note the small intimal plaque, the intact internal elastic lamina and the granulation tissue about the injected fat. *B*, photomicrograph illustrating the changes in the wall of the femoral artery of a dog fourteen days after a mixture of human fat and 16 per cent oleic acid had been injected into the media; × 124. The internal elastic lamina is interrupted and an intimal plaque is continuous into the fibroblastic tissue of the media.

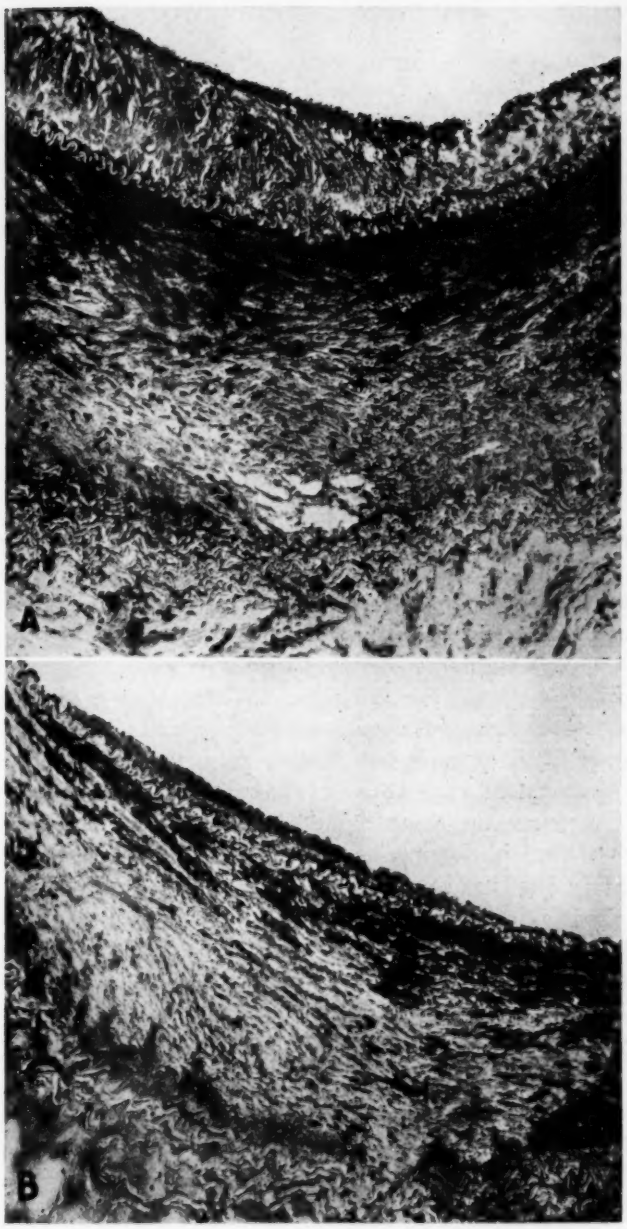

Fig. 2.—*A*, photomicrograph of a large intimal plaque in the femoral artery of a dog; × 124. The wall of the artery had received an injection of an emulsion of human fat and 16 per cent calcium oleate twenty-eight days before death. Note the black deposits of calcium oleate in the medial portion of the adventitia. *B*, photomicrograph illustrating the lesions in the wall of a femoral artery into which a mixture of human fat and 16 per cent stearic acid was injected one hundred and eighty-four days before death; × 124. Note the granular and swollen appearance of the intimal plaque. In the media is a small scar.

Human Fat, 16 Per Cent Stearic Acid and 5 Per Cent Cholesterol Neutralized Over an Aqueous Solution of Calcium Hydroxide.—These lesions were like those produced by a mixture of human fat and oleic acid neutralized over calcium hydroxide.

Control Experiments.—Hemorrhage and trauma were produced by piercing the wall of the artery with a hypodermic needle. Twenty-three arteries were examined one to seventy-seven days later. The extravasated blood was absorbed rapidly; no appreciable tissue changes resulted.

REVIEW OF OBSERVATIONS

All fat mixtures provoked considerable tissue reaction about the site of injection. The resulting granuloma was maximal in one to two weeks. Fatty acids or calcium soaps added to the human fat injected augmented the acute and chronic inflammatory changes. Cholesterol or calcium soaps added to the fat produced more chronic lesions and a larger scar.

Microscopically, the tissue lesions caused by a mixture of human fat and fatty acids were more severe in the first two weeks than those caused by fat alone. But this mixture was absorbed more rapidly and the lesions healed sooner than when only human fat was injected. If the fat contained calcium soaps, similar intense tissue reactions occurred in the first few days. The calcium soaps were slowly absorbed, however, and more chronic lesions resulted than after the injection of a combination of fatty acids and human fat. When the fat contained a small quantity of cholesterol, similar chronic inflammatory lesions resulted. Human fat alone did not evoke foreign body giant cells. Mixtures of fat with fatty acids, calcium soaps and cholesterol produced inflammatory exudates containing many of these cells.

The absorption of fat began in four days or less; in many arteries most of it was absorbed within four weeks. After much fat was absorbed, the proportion of crystalline fat in the globules increased. The crystals were surrounded by clusters of large mononuclear cells and usually small foreign body giant cells. Often with cholesterol long acicular crystals were found in recent and old lesions. In the latter, crystals of fat and cholesterol were embedded in a dense acellular scar. Most of the cholesterol was absorbed gradually, for the Schultz test [8] became less strongly positive the older the lesion.

The inflammatory response about the injected lipid was consistently more marked in the adventitia than in the media. Within forty-eight hours many large mononuclear cells, some laden with fat droplets, were observed about fat injected into the media. They were near dilated capillaries of the media; they probably came from the blood stream. Foreign body giant cells were observed only in the adventitia. In several weeks the scars of the media became inconspicuous and

often could not be identified without the aid of specific stains. The phosphotungstic acid–hematoxylin preparations demonstrated some interruptions of the elastic tissue and replacement of the smooth muscle by a small amount of fibrous tissue.

Fat mixtures injected into the media in 38 arteries produced intimal fibrous plaques in 32 and a disruption of the internal elastic lamina in 23. No secondary fatty changes of these plaques were noted. A few plaques over five months old were nearly acellular and consisted of swollen granular collagenous fibrous tissue that had a slightly mucoid appearance. No definite evidence of deposition of calcium was noted in the healed lesions. Often a little dense granular débris remained which may have been calcium granules or remnants of insoluable fat crystals.

COMMENT

Several interesting observations were made during this study of the lesions resulting in the walls of arteries from injections of known lipids. The character of the lesions seemed to depend on several factors, as discussed by Hirsch.[6b] This dependence concerned mainly the degree of acidity and the solubility of the injected lipids. Fatty acids produced intense acute inflammatory reactions, but the lipids were absorbed readily; therefore, the lesions healed rapidly. Calcium soaps and cholesterol components which were only slightly soluble in human fat and insoluble in tissue fluids often precipitated. As a result, they were absorbed slowly and produced extensive chronic inflammatory changes. The lesions were consistently more marked in the adventitia than in the media.

Lipids injected into the media not only provoked acute and chronic inflammatory reactions in the immediate vicinity but caused degeneration of the overlying internal elastic lamina and development of intimal plaques (fig. 1 *B*). Several investigators produced similar lesions by mechanically injuring the media. Whether intimal plaques would develop without injury to the elastic tissue is difficult to say. In a few specimens where the plaques had formed in the media at the level of the injected fat, the internal elastic lamina appeared unaltered (fig. 2 *A*). Occasionally the lesion of the media caused flattening of the internal elastic lamina without producing an intimal plaque. Cowdry [10] stated that intimal plaques occur spontaneously in animals, especially in dogs; therefore, the assumption that they are caused by injury of an artery may be erroneous. Such plaques were observed occasionally in my experiments, but only in the aorta. The majority of the intimal plaques produced were directly continuous with the medial lesions or in close proximity to the injected fat in the media.

10. Cowdry, E. V.: Arteriosclerosis: A Review of the Problem, New York, The Macmillan Company, 1933.

In the discussion of the factors involved in the production of arteriosclerosis in man much emphasis has been placed on the role of cholesterol. Anitschkow [11] stated that without cholesterol arteriosclerosis could not occur. In my experiments even human fat devoid of cholesterol produced degenerative and inflammatory changes and scars of the media, splitting or rupturing of the internal elastic lamina, and intimal plaques. The addition of cholesterol tended to produce only a more extensive and chronic lesion. Leary [12] suggested that the agent responsible for the stimulation of a marked growth of connective tissue in youths is some soluble product of cholesterol metabolism and not the precipitated cholesterol crystals. However, he believed that in old age when atheromas contain a large quantity of free cholesterol crystals the cholesterol material may stimulate connective tissue growth. Since the cholesterol probably was brought to these regions with solvent fats, it may be that these fats, through a process of hydrolysis or oxidation, liberate fatty acids which alone or in the form of their soaps stimulate the formation of fibroblastic tissues or of an intimal plaque.

During this investigation the absorption of cholesterol occurred slowly, and often large crystals remained embedded in a dense scar. Crystals occasionally were found near remnants of solvent fat globules. Anitschkow observed this relationship of cholesterol crystals and fat globules in healing arteriosclerotic lesions produced in rabbits by a diet high in cholesterol. He thought the fat had infiltrated to help dissolve the cholesterol. Perhaps the fat he observed was a residue of the solvent lipid that had conveyed the cholesterol to the lesion.

Zinserling [13] described primary or spontaneous intimal plaques in dogs. In old dogs they usually were associated with a frayed internal elastic lamina. He observed primary fatty changes of the muscle fibers in the inner third of the media and deposition of fat and cholesterol in the ground substance. Many foam cells were present, and the lesion was surrounded by fibrous tissue. The adjacent internal elastic lamina was frayed; usually there was an intimal plaque. He stated that the usual arteriosclerotic lesion in the dog is a secondary fatty change of the spontaneous intimal plaque; this lesion is combined often with changes in the media. He thought that in some way the plaques favored infiltration of lipids directly from the blood stream. To explain the frequently associated fatty changes in the media he supposed that the fat was carried from the intimal plaque to the media by the lymph channels and absorbed.

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11. Anitschkow, N.: Virchows Arch. f. path. Anat. **249**:73, 1924.
12. Leary, T.: Arch. Path. **17**:453, 1934.
13. Zinserling, W. D.: Beitr. z. path. Anat. u. z. allg. Path. **88**:241, 1932.

There is considerable evidence, however, that the medial lesions in arteriosclerosis may precede the intimal. Duff [14] held that cholesterol compounds from the blood are only secondary in the formation of arteriosclerotic lesions. He regarded some alteration or lesion of the media as primary and stated that this produced changes in the subendothelial tissues favorable to infiltration of lipids from the blood. His assumption was based partly on a study of lesions in the aortas of rabbits. He noted close to the internal elastic lamina spontaneous focal necrosis of muscle fibers before any intimal changes occurred. In the more advanced lesions anisotropic fat deposits were noted in the intercellular ground substance. He observed that in rabbits fed a cholesterol-rich diet the spontaneous lesions became infiltrated with anisotropic lipids much more rapidly than other parts of the aorta. He suggested that sometimes this degeneration of the media produced intimal plaques, or the subendothelial swelling which facilitated infiltration of lipids from the blood. This assumption is substantiated by Ssolowjew [2] and others, who noted that mechanical injury to the blood vessels predisposed to the deposition of lipids in these regions in rabbits fed high cholesterol diets.

Leary [15] studied the early changes in the atheromatous plaques of human arteries. He described a mucoid degeneration of the swollen ground substance of the subendothelial tissues. He expressed the belief that this change may be due to a slight thyroid insufficiency and that it facilitates the deposition of fat. In my experiments some intimal plaques degenerated after five months and had a swollen mucoid appearance.

My studies demonstrate that lipids in the wall of an artery, even those without cholesterol, produce inflammatory lesions of the media and the intima similar to those observed frequently in human arteriosclerosis. It seems that local injury of the media may be the first change in the formation of an atheromatous plaque. The injured region then becomes infiltrated with lipids which in turn stimulate the proliferation of fibroblastic tissue. An important effect of this medial lesion is an alteration of the overlying intima which predisposes to infiltration and deposition of lipids in the subendothelial tissues.

SUMMARY

Lesions were produced in arteries of dogs by injecting into the media human fat, alone or mixed with fatty acids, calcium soaps or cholesterol. The severity and chronicity of the lesions varied with the acidity and speed of dispersal of the fat mixture. Human fat and fatty

14. Duff, L.: Arch. Path. **22**:161, 1936.
15. Leary, T.: Arch. Path. **21**:419, 1936.

acids produced marked acute inflammatory lesions, which healed rapidly because the lipids absorbed readily. Human fat mixed with calcium soaps or cholesterol was absorbed slowly and caused a chronic lesion. Often fat and cholesterol crystals separated, became surrounded by chronic inflammatory exudates, including foreign body giant cells, and finally were embedded in dense acellular scars.

In the formation of arteriosclerotic lesions in man the infiltrating lipids as well as cholesterol may be important in producing fibrous tissue. The products of hydrolysis and of oxidation of the fats are probably responsible for the tissue changes.

Most of the medial lesions produced disruption or splitting of the internal elastic lamina and development of intimal plaques. Thus intimal lesions were secondary to medial lesions simulating the early changes described in arteriosclerosis of man. Injuries of the media may be important in the production of secondary intimal changes which predispose to the deposition of lipids in the early lesions of arteriosclerosis.

Case Reports

LEFT INFERIOR VENA CAVA

BENJAMIN A. GOULEY, M.D., AND PHILIP D. GILBERT, M.D., PHILADELPHIA

The congenital lesion of the heart herein reported is so unusual that we deem it worthy of record. It represents a malformation of the venoauricular structure, the inferior vena cava following the left side of the body and emptying into the left auricle; there was an associated persistent ostium primum. We are unaware of any report of a similar case in Anglo-American literature.

REPORT OF CASE

A full term Negro girl was born Sept. 3, 1936, weighing 9 pounds 6 ounces (4,252 Gm.). The child progressed satisfactorily for eight days, when cyanosis and rapid gasping respiration suddenly developed. There was marked enlargement of the heart, with widening of the area of supracardiac dulness, and a loud systolic murmur was heard over the entire precordium, having its maximum intensity at the pulmonic area. The electrocardiogram showed right axis deviation, which at this age had no special significance. After a temporary response to oxygen therapy, the infant died on the ninth day.

Necropsy revealed passive congestion of the viscera and congenital heart disease. The right ventricle was greatly enlarged; the cardiac apex, formed entirely by the right ventricle, pointed to the right. The left ventricle was comparatively small, only a small portion of it appearing anteriorly.

With the heart in situ, other striking features were noted. One was a structure hanging down over the right lateral ventricular border like a large saddle bag, an extraordinary right auricular appendage. The left auricular appendage was slightly enlarged and globular. Four large vessels arose from the base of the heart. The superior vena cava lay partially posteriorly on the right and was largely obscured. It was normal in all respects, emptying into the right auricle. The three large vascular trunks which occupied the anterior aspect of the supracardiac area were, as appeared from their size and location, abnormal: (1) The systemic aorta, which veered slightly to the right, gave rise at the arch to the three great arteries and after progressive narrowing connected by a patent ductus arteriosus with (2) a very large pulmonary artery, which sent a branch to each lung and continued as the thoracic aorta; (3) a large trunk, forming the left border of the widened supracordium, which extended upward from the left auricle, paralleled the thoracic aorta, arched posteriorly at the same level and continued down along the left side of the aorta into the pelvis as the inferior vena cava, receiving the renal veins and being formed by the junction of two iliac veins.

From the Departments of Pathology and Cardiology of the Philadelphia General Hospital.

Section of the heart revealed a persistent ostium primum. The right auricle was enlarged, and its elongated appendage almost reached the apex of the heart. Hepatic veins emptied into the right auricle, and normal pulmonary veins emptied into the left. The inferior vena cava entered the upper lateral portion of the left auricle almost at the junction of the latter with the auricular appendage. Its entrance was unguarded by any valve formation.

The hepatic veins were anomalous. Rather large veins extended upward over the anterior aspect of the liver and passing through the diaphragm reached the right auricle (fig. 1). Another smaller vein came up from the posterior aspect of the liver, at approximately the same level as the anterior vein, and joined the latter on entering the right auricle. These hepatic veins had no connection with

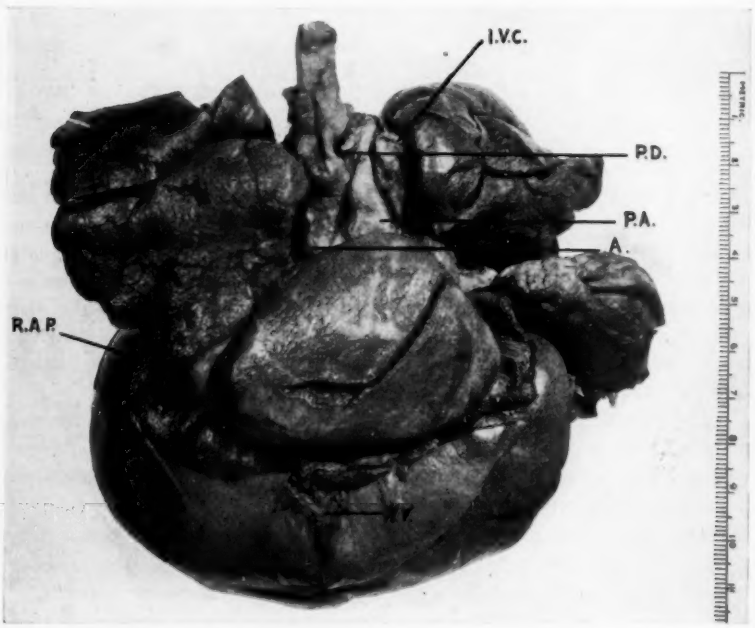


Fig. 1.—Heart, great vessels, lungs and liver. The heart turns to the right (dextrocardia). Extending down almost to the cardiac apex is a rounded baglike structure, the right auricular appendage (*R. Ap.*). The superior vena cava is obscured by the right lung, but three large vascular trunks are seen at the base of the heart, namely, the aorta (*A*), the pulmonary artery (*P. A.*) and the inferior vena cava (*I. V. C.*); the last enters the left auricle. A patent ductus arteriosus (*P. D.*) connects the narrowed aorta with the pulmonary artery, which below this point (obscured) has given off arterial branches to both lungs. Aberrant hepatic veins from the anterior surface of the liver (one is opened, *H. V.*) course upward through the diaphragm to reach the right auricle.

any other venous system as far as could be determined. The liver itself was of unusual shape, its anterior aspect having a marked convexity; the lower border was without a definite edge, the anterior and inferior aspects rounding into each other.

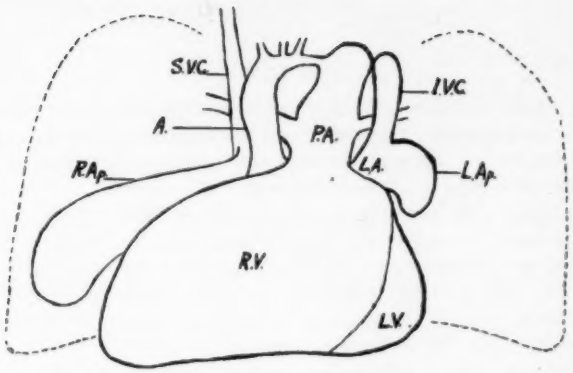
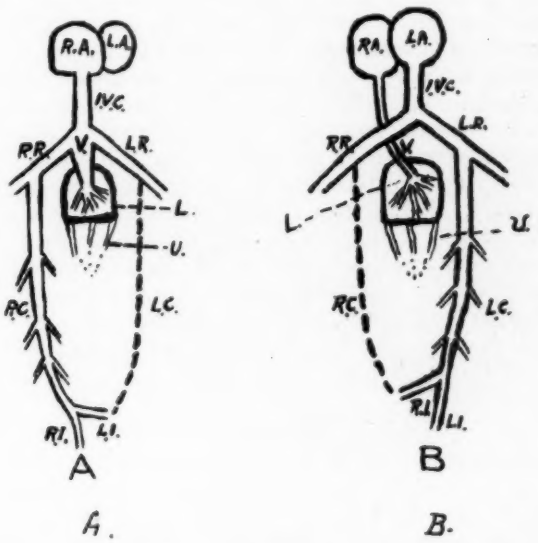


Fig. 2.—A schematic drawing of the heart showing some structures not seen in figure 1. The inferior vena cava enters the left auricle (*L. A.*) at the junction of the latter with its appendage (*L. Ap.*); the other parts are the superior vena cava (*S. V. C.*), the right ventricle (*R. V.*), the left (*L. V.*) and the right auricular appendage (*R. Ap.*).



A. *B.*

Fig. 3.—*A*, normal development of the inferior vena cava. The posterior right cardinal vein (*R. C.*), its branch the right renal vein (*R. R.*) and the ductus venosus (*V*) join to form the inferior vena cava (*I. V. C.*), which empties into the right auricle (*R. A.*). The posterior left cardinal vein (*L. C.*) disappears and is represented by a dotted line. At its beginning there is survival of a branch (*L. R.*), the left renal vein, and at its very end there is another cross branch (*L. I.*), the future left common iliac vein. *B*, the apparent maldevelopment in our case of a left inferior cava. The right cardinal vein (*R. C.*) is atrophied, only its cross branches *R. R.* and *R. I.* surviving. The left cardinal vein (*L. C.*) is dominant and leads directly into the left auricle (*L. A.*). The hepatic veins (liver, *L*) deriving from the original ductus venosus (*V*) empty directly into the right auricle (*R. A.*). Small veins leading up to the liver are the umbilical and vitelline veins (*U*), undergoing postnatal atrophy.

COMMENT

The persistent ostium primum, while uncommon, has been fully discussed in many reports. The more interesting and really unique anomaly was the inferior vena cava of the left side. In the absence of reports of similar cases we venture an explanation.

The presence of a left inferior vena cava is indicative of an abnormal development in the embryo of the cardinal venous system, particularly of the posterior cardinal veins which drain the lower half of the embryo. Normally, the right lower portions of the posterior cardinal and the subcardinal veins merge, forming a large trunk which in turn unites with the terminal portion of the ductus venosus to form the inferior vena cava. The left posterior veins degenerate and disappear, only their very foremost and lowermost portions surviving to form cross branches with the right cardinal veins, eventually becoming, respectively, the left renal and the left common iliac vein. Evidently, a reverse development occurred in this case, the right posterior cardinal and subcardinal veins disappearing, while the left enlarged and remained as the inferior cava. However, with this survival there appears to have been a further maldevelopment of the venous connection with the heart. The left cardinal vein did not join the terminal end of the ductus venosus; rather it emptied directly into the left auricle. The hepatic venous system remained isolated, draining directly into the right auricle. Unfortunately, the azygos veins were not studied. Such congenital defects must develop very early in embryonic life, probably in the third and fourth weeks (compare Piersol's reconstructions of the human embryo drawn from the His [1] models). Persistence of the ostium primum is also an early developmental defect, possibly occurring simultaneously in this case as part of a widespread maldevelopment of the auriculovenal structure. The presence of the patent ductus arteriosus was distinctly in the nature of a compensatory mechanism, otherwise postnatal life would have been impossible. It is interesting to note that cyanosis was absent for eight days, appearing shortly before death.

SUMMARY

A full term infant, apparently in good health, became cyanotic on the eighth day of life. Marked transverse cardiac enlargement and a loud systolic murmur over the entire precordium were noted. Death occurred on the ninth day. Necropsy revealed a persistent ostium primum, an inferior vena cava on the left side, entering the left auricle, and hepatic veins that emptied directly into the right auricle.

1. Piersol, G. A.: Human Anatomy, ed. 5, Philadelphia, J. B. Lippincott Company, 1916, vol. 1, p. 706.

PLASMACYTOMA OF THE UPPER PART OF THE RESPIRATORY PASSAGE

CHARLES M. CAMPBELL JR., M.D., AND FRANCIS C. NEWTON, M.D., BOSTON

The case under consideration is one of plasmacytoma of the upper part of the respiratory passage and is being reported because of the relative rarity of such an occurrence. It is typical in all respects of the majority of the cases presented in the literature. As there are several excellent recent reviews of the previously reported cases, it is felt that a comprehensive review of the literature at this point would be superfluous. Mattick and Thibaudeau [1] published such a review in connection with the report of a case which came under their observation. Two other reviews of the material which are of a comprehensive nature are by Claiborn and Ferris [2] and Blacklock and Macartney,[3] each of which was written in connection with a report of additional cases. Two cases reported by Jackson and his associates [4] and a case reported by New and Harper,[5] not included in the aforementioned reviews, bring the total number of reported cases up to 23.

REPORT OF A CASE

A consulting engineer 62 years old entered the Peter Bent Brigham Hospital for the first time on April 6, 1938, because of loss of strength, diarrhea and cough of six weeks' duration. Forty years previously he had an attack of fatigue and malaise associated with palpitation, which was diagnosed as neurasthenia and was improved by rest. Seven years before admission a similar episode associated with diarrhea occurred. Six weeks before admission, feeling "run down," he started on a sea cruise for a rest. Following the resultant sea sickness, for three weeks he was nervous and upset and had loose diarrhea, free from blood or mucus. Shortly thereafter a cold developed with coryza and a productive bronchial cough, accompanied by slight pain in the left side of the chest. During this illness he first became aware of small polypoid masses in back of the uvula. On examination five or six solid red polypi, ranging in size up to nearly 1 cm. in diameter, were seen arising from the posterior tonsillar pillars on either side. There were signs of fluid at the base of the left lung and there was roentgen evidence of pulmonary tuberculosis on that side. Roentgen studies of the bones showed no evidence of metastatic tumor. The diagnosis of tuberculosis was confirmed by injection of the pleural fluid into guinea pigs. The urine showed no Bence Jones protein. The Hinton and Wassermann tests were negative. Other laboratory findings were essentially noncontributory. April 21 the polypi and surrounding areas of mucous

From the departments of pathology and surgery of the Peter Bent Brigham Hospital.

1. Mattick, W. L., and Thibaudeau, A. A.: Am. J. Cancer **23**:513, 1935.
2. Claiborn, L. N., and Ferris, M. W.: Arch. Surg. **23**:477, 1931.
3. Blacklock, J. W. S., and Macartney, C.: J. Path. & Bact. **35**:69, 1932.
4. Jackson, H.; Parker, F., Jr., and Bethea, J. M.: Am. J. M. Sc. **181**:169, 1931.
5. New, G. B., and Harper, F. R.: Arch. Otolaryng. **16**:50, 1932.

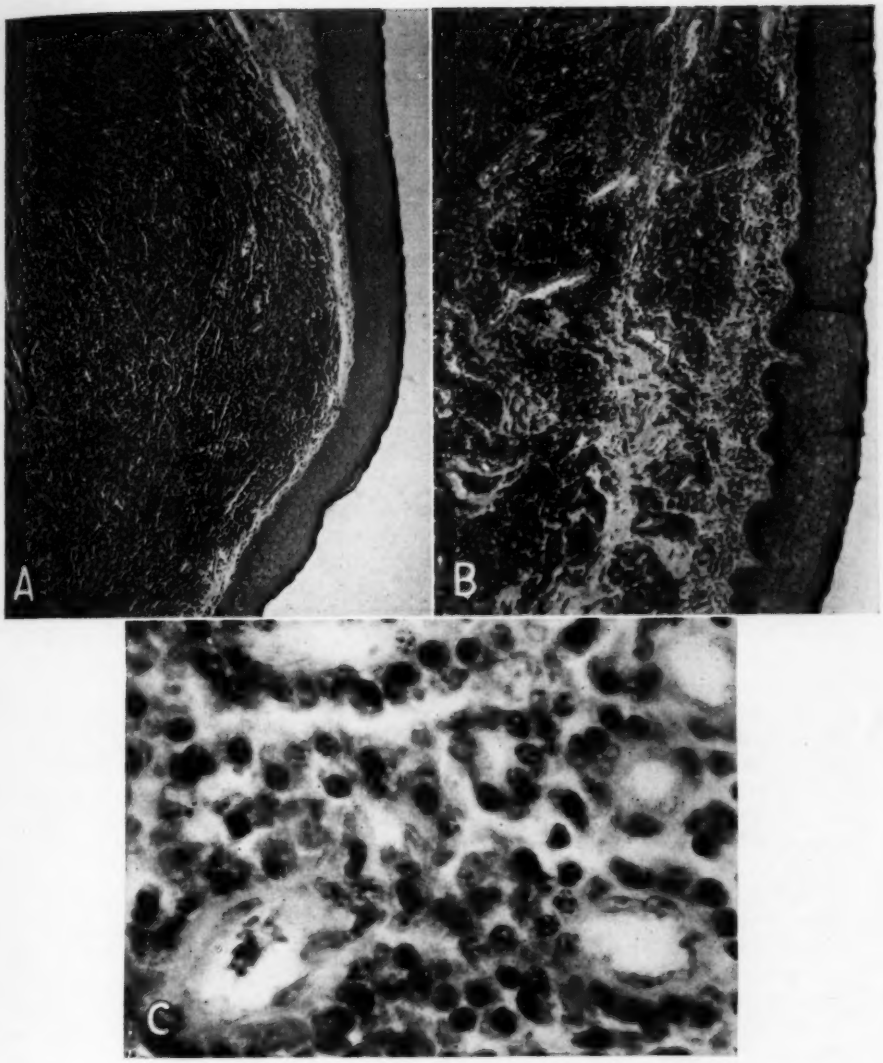
membrane were removed. He was discharged May 7 and went to a sanatorium for treatment of his tuberculosis. Word was received from that institution in July that several small nodules had been removed from the upper part of the respiratory tract and microscopic slides of these lesions were submitted to Dr. S. B. Wolbach for comparison with the original sections.

Pathologic Examination.—At the first operation 6 specimens were received in the pathologic laboratory. These fragments consisted of mucous membrane to which were attached numerous small pedunculated nodules, four of which together, representing the largest group, measured 1.4 by 1 by 0.5 cm. These nodules were of a pinkish yellow color and of a firm rubbery consistency. On sectioning, the cut surface of these nodules was seen to be homogeneous and translucent. There was no evidence that these small tumor masses infiltrated the underlying musculature or the overlying mucosa. A small fragment of one of the nodules was immediately frozen and sectioned. When stained by Giemsa stain, it presented the typical picture of plasmacytoma, with plasma cells densely arranged. The remaining tissue was fixed in part in solution of formaldehyde U. S. P. (1:10) and in part in Zenker fluid with 5 per cent glacial acetic acid. Four sections of material fixed in Zenker fluid were stained with eosin-methylene blue and one with Mallory's phosphotungstic acid-hematoxylin. One of these sections consisted of a thin strip of mucous membrane with a small nodule of sharply circumscribed tumor tissue at each end. These nodules were densely cellular, and under higher magnifying power the cells were seen to be for the most part typical plasma cells, with rough or slightly oval nuclei in which the chromatin was arranged in small dark masses giving the cart wheel or clock face appearance. The finely granular cytoplasm stained light bluish purple. Most of the cells showed paranuclear rarefaction of the cytoplasm, and in these areas the tissue was pink rather than blue. No mitotic figures could be found, but a few cells contained two, rarely more, nuclei. The stroma was very delicate, and in the section stained with phosphotungstic acid–hematoxylin it appeared as a very fine fibrillary network. Around the delicate capillaries the cells were frequently arranged in an acinar-like arrangement, a feature which in the frozen sections gave a confusing resemblance to carcinoma. No definite capsule surrounded the tumor cells, but these did not invade the surrounding tissue. The overlying mucosa was free from evidence of ulceration, and the strip of mucosa between the two nodules was free from abnormal cellular infiltration.

A second section showed a group of four or five small nodules separated by thin strands of moderately dense connective tissue. The tumor nodules resembled those in the preceding section except for a greater number of pyknotic nuclei. This section showed the same absence of infiltration of surrounding tissue by plasma cells.

The third section consisted of a small fragment of tonsil attached to skeletal muscle and connective tissue. No portion of the tumor was included. In the subepithelial connective tissue covering the muscle there was a slight infiltration by lymphocytes, representing a chronic inflammatory process. Among these lymphocytes the plasma cells were more numerous than they usually are in chronically inflamed tissue of this region. Around the follicles of the tonsillar tissue were also seen a few areas of chronic inflammation, and these areas also showed more plasma cells than do the follicles of other chronically inflamed tonsils.

The fourth section stained by this method added no information to that obtained from the three other sections.



A (× 65; eosin–methylene blue) shows the nonencapsulated but moderately distinct edge of the tumor. There is no invasion of the epithelium, which is free from ulceration.

B (× 65; eosin–methylene blue) shows a slight chronic inflammatory change of the subepithelial tissue. The cells in the immediate subepithelial tissue vary from those lying deeper, in that the latter are exclusively plasma cells whereas the former show a heavy admixture of lymphocytes (not shown at this magnification).

C (× 680; eosin–methylene blue) shows that all the cells are typical plasma cells with clock face nuclei. Frequently the paranuclear zone of clear cytoplasm is seen. Note the perivascular arrangement of the cells and the absence of mitotic figures.

Of the material fixed in solution of formaldehyde, one section was impregnated by the method of Levaditi, while the other was stained by the Ziehl-Neelsen method. Careful search of these slides failed to reveal any spirochetes or any acid-fast bacilli.

The tissue submitted from the sanatorium to which the patient had gone for treatment of his tuberculosis was examined by Dr. Wolbach and was reported by him to be morphologically identical to that removed earlier.

COMMENT

Cases of extramedullary plasmacytoma are rare according to reports in the literature. Of such cases, 23 have been reported in which the tumor occurred in the upper part of the respiratory tract; the present case brings the number to 24. The common feature in these 24 cases was the presence of plasma cells densely arranged in discrete nodules. The sex incidence reveals that such tumors occur predominantly in men, 21 of those reported having been found in men and but 3 in women. The majority of the patients were in the fifth and sixth decades of life, but the age of incidence ranges from 20 to 69 years. These generalizations as to the relation of incidence to age and to sex cannot be taken as necessarily valid, because of the small number of cases in the series. Review of the cases showed no other clinical factor to be correlated with the appearance of the tumor. In several of the reported cases the patient was syphilitic, but there is no close correlation between the disease and syphilis, nor can any relation to tuberculosis or any other specific chronic granulomatous disease be discovered.

The pathologic features in the cases reported to date show considerable variation. In 5 of the 24 cases the growth was definitely granulomatous, but these cases must be included in the series because of such features as the density of the plasma cells and the absence or scarcity of other cell types, which serve to differentiate these granulomatous growths from other granulomas and to liken them to the true neoplasm which the other cases represent.

Of those lesions which were definitely neoplastic, only 4 can be considered malignant on the basis of local invasiveness or metastasis to distant organs. The others, it has been assumed, were benign because of the absence of these characteristics. However, in 8 of 16 of the cases, including the present instance, the growth recurred locally after excision. In the remaining 8 cases the patient was not followed long enough after treatment to find whether or not there was recurrence.

In regard to treatment, surgical removal and irradiation are the two methods which have been tried. Radium and roentgen rays together caused marked shrinkage of the tumor in Kaufmann's [6] case. Claiborn and Ferris followed surgical excision by 33.75 millicurie hours of irradiation, and in their patient no recurrence had taken place in seven months. New and Harper used radium and roentgen rays in combination, which resulted in complete disappearance of the tumor over a period of several months. The most common mode of treatment is excision, but this has not proved entirely satisfactory because of the frequency

6. Kaufmann, E.: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 1, p. 272.

of recurrence. The series of cases is too small to use as a basis for a dogmatic statement, but the results suggest a combination of thorough surgical removal with subsequent irradiation as the most promising type of treatment.

SUMMARY AND CONCLUSIONS

A case of small plasma cell tumors occurring in the upper part of the respiratory passage of a 62 year old man is reported. These tumors recurred after surgical excision, but the absence of distant metastases and of local invasiveness indicates that the tumors were benign.

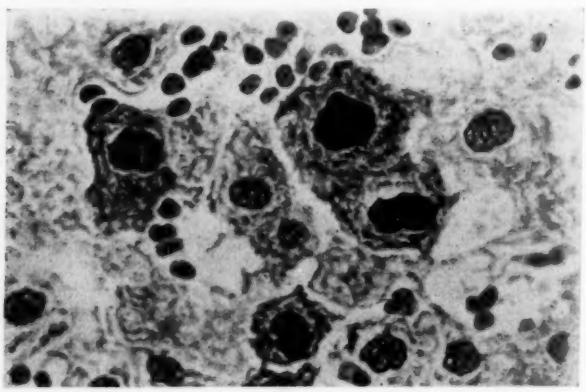
Laboratory Methods and Technical Notes

PONCEAU-FUCHSIN STAIN FOR ANDROGENIC ADRENAL CORTICAL CELLS

A Modified Technic

T. F. Fujiwara, M.D.,* Cleveland

Although the association of hypertrichosis and adiposity with tumor of the adrenal gland was established as long ago as 1756 by W. Cook,[1] it was not until 1933 that a reasonably specific stain differentiating the tumors of androgenic origin from the other types of adrenal cortical tumors was discovered by H. W. C. Vines.[2] His ponceau-fuchsin stain



Photograph of a colored microdrawing to show the deeply fuchsinophilic character of the so-called androgenic cells.

is claimed to be specific for the cells of androgenic origin, not only for those in the cortical tumors of the adrenal glands giving rise to the androgenital syndrome but also for those in fetal adrenal glands, particularly in the adrenals of the male fetus between the ninth and seventeenth weeks.

A white unmarried woman 23 years old was admitted to the University Hospitals, to the service of Dr. Charles Hudson, with the classic manifestations of the androgenital syndrome. A benign adrenal cortical adenomatous tumor, with the

* Hanna Research Fellow in Pathology.

From the Institute of Pathology, Western Reserve University and University Hospitals.

1. Broster, L. R.: Arch. Surg. **34**:761, 1937.

2. Broster, L. R., and Vines, H. W. C.: The Adrenal Cortex: A Surgical and Pathological Study, London, H. K. Lewis & Co., Ltd., 1933.

flattened adrenal gland attached, was removed surgically by Dr. James Joelson. The entire specimen weighed 135 Gm. The convalescence was uneventful and was followed by marked improvement in the condition of the patient. Sections from the tumor stained with the ponceau-fuchsin stain, by a modified technic, gave a strongly positive reaction. Similarly prepared sections of adrenal tissue from normal males and females of varying ages and of benign and malignant adrenal cortical tumors from patients not manifesting the androgenital syndrome all gave a negative staining reaction. As with the Vines stain, a weak reaction was found in the interstitial cells of the testis, the corpus luteum and the anterior lobe of the pituitary.

PREPARATION OF THE MATERIAL

The material to be examined is fixed for a period of twelve to twenty-four hours in Zenker's fluid containing solution of formaldehyde U. S. P. instead of acetic acid. In order to facilitate proper fixation, the tissue should not be over 3 to 4 mm. in thickness. It should not remain in the fixing fluid for more than twenty-four hours. Best results are obtained when the volume of the fixative exceeds the volume of the tissue at least thirty times. The tissue is then washed in running water for a period of twenty-four hours, after which it is embedded in paraffin and sectioned in the usual manner.

TECHNIC FOR THE PONCEAU-FUCHSIN STAIN

1. Put sections through xylene, alcohol and water in the usual manner.
2. Stain with ponceau-fuchsin five minutes (solution A, 2 parts; solution B, 1 part).

Solution A is made up as follows:

Ponceau de xylidine (Krall)	1 Gm.
Glacial acetic acid	1 cc.
Distilled water	100 cc.

Solution B is made up as follows:

Acid fuchsin	1 Gm.
Glacial acetic acid	1 Gm.
Distilled water	100 cc.

3. Rinse in distilled water.
4. Differentiate in a saturated aqueous solution of trinitrophenol (approximately five minutes). One per cent phosphomolybdic acid may be used instead of trinitrophenol.
5. Rinse in distilled water.
6. Dehydrate, clear and mount in salicylate balsam.

In step 4, the weak acid rapidly decolorizes the negative, or nonfuchsinophilic, cells, while the positive, or fuchsinophilic, cells retain the stain for a considerably longer period. In staining an unknown tissue it is advisable to control the degree of differentiation by simultaneously staining a section from a normal adrenal gland or from the anterior lobe of the pituitary or preferably sections from both. The proper differentiation will have been obtained when the control section has been completely decolorized.

General Reviews

VENEREAL LYMPHOGRANULOMA

RIGNEY D'AUNOY, M.D.
AND
EMMERICH VON HAAM, M.D.
NEW ORLEANS

CONTENTS

A comprehensive review of venereal lymphogranuloma has not appeared in American literature. Hugh Stannus' excellent monograph and his supplementary articles appearing in the *Tropical Disease Bulletin* are the only exhaustive treatises on the disease in the English language. Most modern textbooks deal with venereal lymphogranuloma only briefly, and even special monographs on genitourinary infections contain numerous erroneous conceptions regarding the etiologic and pathologic aspects of this disease.

Our intensive study of venereal lymphogranuloma, extending now into its sixth year, afforded us ample opportunity to become familiar with most of the problems presented by the disease and to make many important observations regarding its causal agent, clinical manifestations and pathologic character. We wish to correlate the information previously presented, record the results of our more recent studies and briefly review such important matters as: the history of venereal lymphogranuloma; the geographic distribution and incidence; the clinical manifestations; the pathologic lesions; the biologic characteristics of the causal agent, and the various methods of diagnosis and therapy.

HISTORICAL REVIEW

A historical review of venereal lymphogranuloma is difficult because of the numerous names given the various lesions of the disease before their recognition as manifestations of a distinct clinical entity. To provide proper insight into the history of venereal lymphogranuloma, we deem it best to present the important early contributions dealing with the subject in chronologic order.

Probably the earliest mention of and description of the lesions of venereal lymphogranuloma are found in Wallace's "Treatise on Venereal Diseases," published in 1833. The author gave an accurate word picture

From the Department of Pathology and Bacteriology of the School of Medicine, Louisiana State University, and the Charity Hospital of Louisiana.

of the inguinal bubo with its accompanying constitutional symptoms. Unaware of the true cause of the lesion, he classified it as an "indolent primary syphilitic bubo" and stressed its slow healing and the characteristic involvement of the skin. Eleven years later Desruelles gave an excellent description of 2 cases of vulvar hypertrophy following primary involvement of the inguinal glands. Stannus gave Huguier credit for the first description of this lesion (1848), and Huguier's appellation of it (esthiomène) is still used as one of its many designations. Huguier undoubtedly recognized and correctly described for the first time the characteristic induration and discoloration of the affected parts, with the later ulceration and loss of tissue so typical of vulvar hypertrophy. That same year Larsen published the first description of inflammatory stricture of the rectum. All the patients he had observed with stricture of the rectum were females, and he attributed the lesion, which he termed "hyperplastic infiltration of the rectum," to syphilis.

In Europe during the second half of the nineteenth century numerous reports concerning the strumous bubo or *bubon d'emblée* appeared, the lesions in most instances being considered syphilitic. However, Stannus expressed little doubt that "these authors were dealing with cases of lymphogranuloma inguinale." Velpeau described the formation of multiple abscesses in inguinal adenitis, and Reder emphasized that the majority of his patients so affected were males. Nélaton was the first to express the belief that this peculiar inguinal lesion was the manifestation of a new and unknown disease and suggested that the so often accompanying small penile lesions were the sites of entry of its causal agent.

Trousseau described as a not uncommon lesion among the male natives of the islands of Réunion and Mauritius, in the Indian Ocean, unilateral or bilateral inguinal buboes which frequently showed suppuration and often lasted a year or longer. Similar lesions were reported in other colonial territories and were attributed to malaria by some authors (Martin; Ségard). The theory that "climatic influences" of the tropics could cause inflammation of the inguinal glands induced Ruge in 1896 to speak of the lesions as "climatic inflammation of the inguinal glands" and caused Godding to introduce the term "climatic bubo," still found in medical literature. The latter also mentioned superficial penile lesions as possible portals of entry of the infection.

In the United States, similar glandular lesions were described in Philadelphia by Platt, in Baltimore by Winslow and Jones and in Memphis, Tenn., by Armstrong. Klotz in 1890 published a paper, entitled "Strumösen Bubonen," in which he described the classic local and constitutional pictures of the disease from study of some 120 cases encountered over a period of ten years in the German Hospital of New

York. In most of his cases a small penile lesion was present, which he regarded as the point of entrance of the noxious agent producing the bubo. During excision of such a bubo he became infected, large axillary buboes developing.

While the foundation was thus laid for the recognition of "strumous" and "climatic" buboes as manifestations of venereal lymphogranuloma, the causes of esthiomène and of inflammatory stricture of the rectum remained shrouded in darkness. Since Huguier's complete description of esthiomène, numerous reports of similar cases had appeared, syphilis or tuberculosis being ascribed as the cause of the lesions. The principal argument for the syphilitic nature of vulvar elephantiasis was the fact that in the majority of cases there was a history of syphilis, though the complete failure of antisyphilitic treatment tended to disprove the argument. Fournier discussed such tumefaction of the vulva under the name "sclerotic induration of the vulva" in his monograph on syphilis in 1873, and Martineau cited similar cases in his description of syphilitic lesions of the vulva. I. Taylor and MacDonald expressed the belief that the disease was tuberculous and classed it as "lupus of the vulvo-anal region." Bender, in his treatise on tuberculosis of the vulva, recorded many cases of ulcerative lesions of the organ in which the finding of acid-fast organisms was the only basis for the diagnosis. In a critical review of Bender's work, Stannus pointed out that the occurrence of such organisms on the external genitalia is not uncommon, stressing the necessity of properly identifying them as tubercle bacilli by inoculation of animals. Koch in 1896 published 20 cases of "ulcus vulvae chronicum elephantiasicum," emphasizing the sclerotic nature of the disease and the frequent involvement of the perineum and rectum. In his opinion the disease was caused neither by syphilis nor by tuberculosis, a point of view shared also by Pescione. R. W. Taylor attributed tumorous growths on the vulva to simple hyperplasia induced by irritation and trauma, and Verchère expressed the opinion that any venereal disease or tuberculosis could cause elephantiasis of the vulva. Chancroidal, gonorrheal and streptococcic infections were also considered as etiologic factors in the production of vulval hypertrophy (Stannus).

Inflammatory stricture of the rectum caused by the virus of venereal lymphogranuloma presents such a typical clinical picture that descriptions of the lesion can be readily recognized in the medical literature of the nineteenth century even though appearing under various names. Most of the authors of the nineteenth century, basing their conclusions partly on the history of the patients and partly on the histologic picture, held that the lesion was caused by syphilis. Godebert, in his thesis on rectal stricture, stated that he had elicited a history of syphilis in 47 of 67 cases, and Mathews believed that in 60 per cent of his cases of rectal stricture the condition was due to syphilis. Fournier, in his monograph

"The Tertiary Lesions of the Anus and the Rectum," gave a good description of the anorectal syndrome of venereal lymphogranuloma and stressed the cylindric shape of the stricture and the rigid thickening and infiltration of the rectal wall. He named the lesion *syphilome ano rectal,* confessing, however, that his opinion concerning its nature was merely hypothetic. Bryant was inclined to believe that syphilis as a cause of stricture of the rectum was by no means unusual, and only Delbet and Mouchet, Koch and a few others expressed differing opinions. Wallis and also Goodsall and Miles expressed the opinion that ulcerations with superimposed infection were responsible for the development of rectal strictures. Tuberculosis and chancroidal infections were considered as significant etiologic factors by Sourdelle. The lack of recorded cases of esthiomène of the pudenda and rectal stricture among the natives of tropical countries during this period can be explained on the ground that such lesions remained unrecognized or that the patients, mostly prostitutes, shunned medical aid.

From this brief survey it can be seen that all principal lesions of venereal lymphogranuloma had been observed and properly described in the nineteenth century. However, although few contemporaries claimed that there was here a "new and unknown" disease, the true interrelationship of the lesions, the mechanism of infection and the causal agent were unknown.

During the early part of the twentieth century reports on the occurrence of climatic buboes in various colonial possessions became more frequent, as evidenced by the communications of Pigeon and Tanton (290 cases), Priado (50 cases), Müller and Justi (30 cases) and Günther (35 cases). The venereal nature of the infection was pointed out by Rost and others, and intercourse with native women was held responsible for its spread in tropical seaports (Treibly). In 1913 Durand, Nicolas and Favre published the reports of their exhaustive studies on "les adénites inguinales à foyers purulents intraganglionnaires." In these, the importance of small herpetiform penile lesions as portals of entry of the causal agent was stressed, and a thorough description of the glandular lesions was given. Because of the histologic resemblance to the lesion encountered in Hodgkin's disease, Durand and his co-workers named the condition "lymphogranuloma inguinale," a term which under various modifications is used extensively in modern literature. Recently Sulzberger and Wise proposed the name "lymphopathia venereum" for this disease, and Wise prefers to call it "lymphogranuloma venereum." In the English literature (Stannus and others) "inguinal lymphogranuloma" or "lymphogranuloma inguinale" is used. Since the National Conference on Nomenclature of Disease has adopted the term "venereal lymphogranuloma" as the official name of the disease, we use it in the present review except in instances in which correct quo-

tation from the literature demands another term. Since this disease is distinctly venereal in character, producing granulomatous lesions principally located in the lymph glands and along the infected lymphatics, we believe that the name adopted here covers the characteristic features of the infection better than any other suggested so far. Certainly the manifestations in the female have little or nothing to do with the inguinal region.

Investigations of this disease were interrupted during the World War but were resumed to some extent after 1920. In 1922 Phylactos publishd a thesis on the subject, quoting extensively the work of Durand, Nicolas and Favre. In the same year W. H. Hoffmann, as well as Chastang, discussed the possible interrelationship between venereal lymphogranuloma and climatic bubo. Gougerot, on the basis of 20 cases, still maintained that elephantiasis of the vulva was tuberculous, while Stein and Heimann reported a series of similar cases with rectal involvement under the diagnosis of "luetic proctitis and periproctitis." Symonds in 1923 observed 7 cases of what he believed to be "gonorrheal stricture of the rectum" but which according to Stannus were probably venereal lymphogranuloma, and Lockhart-Mummery that same year took a definite stand against the widely publicized opinion that syphilis was the most common cause of stricture of the rectum, contending that it rarely was. Bory in 1928 discussed the importance of Bacillus subtilis in the etiology of the Nicolas-Favre disease.

Of tremendous importance to the further development of a more comprehensive understanding of venereal lymphogranuloma as a clinical entity was the discovery by Walter Frei in 1925 of a specific cutaneous reaction resulting from the infection. He showed that an intracutaneous injection of 0.1 cc. of diluted pus taken from the buboes of human venereal lymphogranuloma and sterilized by fractional heating produced in all those affected or who had been affected with the disease marked induration with erythema at the site of injection, reaching its maximum in forty-eight hours. He claimed that when the test was properly performed, the reaction possessed a high degree of specificity for venereal lymphogranuloma. The same year Frei established the connecting link between climatic bubo and venereal lymphogranuloma by demonstrating that an antigen prepared from either lesion gave a positive reaction in a patient afflicted with either condition. Three years later, with Koppel, he obtained positive reactions with Frei antigen in 5 persons with genitoanorectal syndromes. Koppel and many other authors also obtained positive skin reactions in a large number of patients with vulvar elephantiasis and uncomplicated rectal stricture, thus proving the etiologic correlation between these clinical syndromes. Potent antigens were also prepared from the tissues of chronic lesions by de

Gregorio and Murúa, by Nicolas, Favre, Lebeuf and Charpy and by Wiese and Klestadt.

The next achievement in the study of venereal lymphogranuloma was the discovery of the causal agent by Hellerström and Wassén in 1931. After many negative or doubtful reports of successful transmission in animals (Darré and Dumas; Ravaut and co-workers), these Swedish authors succeeded in producing lesions by injecting intracerebrally into certain species of monkeys pus obtained from buboes of patients suffering with venereal lymphogranuloma. From these experimental lesions a filtrable virus was regularly obtained with which the disease could be produced by continued passage in animals. A virus showing identical biologic and physical properties was then isolated from the primary human lesions (Löhe, Rosenfeld, Schlossberger and Krumeich, 1933); from climatic buboes (Findlay, 1933); from tissues taken from chronic lesions—esthiomène and inflammatory stricture of the rectum—(Ravaut and co-workers; Laederich, Levaditi, Mamou and Beauchesne).

The brilliant work of Frei, Hellerström and Wassén, Levaditi and their co-workers cleared the mystery presented by the complexity of lesions caused by this filtrable virus and stimulated further recognition of the disease in all parts of the world. With the nature of its causal agent known and with the help of the diagnostic Frei reaction, nothing should prevent thorough investigation of the mode of infection and spread, the clinical manifestations, the complications, the prevention and the methods of treatment of venereal lymphogranuloma.

GEOGRAPHIC DISTRIBUTION AND INCIDENCE

World Wide Distribution.—Venereal lymphogranuloma in its various manifestations can be found in all quarters of the globe but is more prevalent in tropical, subtropical and temperate climates. On the European continent it is found in probably all of the larger cities, the number of reported cases being steadily on the increase. It is endemic in North and South America, Asia and Australia and along the coasts of Africa.

Hellerström and Wassén in 1933 sent a questionnaire to some 350 clinics for patients with dermatovenereal diseases and collected as a result approximately 1,800 cases of the disease in its various manifestations. Cormia in 1934 estimated the number of reported cases to be about 2,000. During the last two years that number has been at least doubled. We have observed over 600 cases in our venereal diagnostic clinic, and many other series of from 50 to 150 cases have been reported by Navarro Martin, de Gregorio, Advier and Riou, Kalz and Sagher, Pautrier and Weiss, and others during this period. The question arises as to whether this apparent increase in the disease is caused by the

greater ease of its diagnosis and the fact that medical investigators have become more lymphogranuloma conscious or whether there is actually an increase in the number of patients due to rapid spread of the disease. We have shown that in New Orleans at least the first conclusion seems correct, as photographs and descriptions of inguinal lesions contained in old charts from the Charity Hospital at New Orleans leave no doubt but that the disease was observed frequently in New Orleans thirty years ago.

The International Bureau of Public Hygiene of the League of Nations attempted to investigate this problem and sent questionnaires on the subject to the leading venereologists of the European continent. While Jitta of Holland, in response to the questionnaire, did not believe that venereal lymphogranuloma is a public health problem of great importance, venereologists in other countries, especially Germany and Rumania, reported a steady increase of the disease during the past years. The statistics published by Ionesco-Mihaiesti and Longhin are particularly alarming. From 10 cases in 1930 in the city of Bucharest, the capital of Rumania, the number increased over the next three years to 281, and while no cases in females were reported in 1930, 70 were reported in 1933. Reiter recorded 200 cases in Berlin and 100 cases in Breslau, Germany, during the period from 1929 to 1934. Nicolau expressed the opinion that lack of efficient treatment and of prophylactic control of the disease explained this rapid increase, and Koch predicted for the same reasons a higher incidence in the future. Ruge stated that in Hamburg, Germany, during the years 1921 and 1928 the number of cases increased by from 2 to 39 each year, and Frei estimated that between 300 and 400 cases occurred yearly in Berlin. Gougerot and Burnier observed only 9 cases during 1934, in contrast to 389 cases of syphilis. Gibson reported that in the year 1931, 733 inguinal buboes were seen in the English Navy. Many cases of venereal lymphogranuloma have been reported from Italy (Midana and Vercellino; del Vivo), Spain (Bejarano and Gallego Calatayud, Barriola and Maneru, and others), Czechoslovakia (Kalz and Sagher), Russia (Levinson), Sweden (Hellerström) and Norway (Wefring). Perkel and Sourgik stated that the disease occurred along the coast of the Black Sea. Rajam reported cases from India; Tran-Tan-Phat, from Indochina, and Massias, from Cochin China. There are numerous cases reported from China and Japan (Gray and Yieh; Wang and Shen; Kitagawa) and from the Dutch Indies (Bonne and co-workers; Honna and Sasaki). In Africa cases have been observed along the coast of the Belgian Congo (Chesterman), in Tanganyika (Graham), in Algiers, Algeria (Lasnet), in Morocco (Moutot) and in Dakar and surrounding territory (Advier and Riou). The disease is known in South, Central and North America and in Australia (Priado). Coutts, who has studied venereal lymphogranuloma

extensively in Chile, expressed the opinion that it was known to the Romans, Greeks and Arabs and was imported to the New World by the white settlers and slaves. In the Argentine Republic (Zorraquin; Bachmann), Brazil (Crisculo), Venezuela (de Bellard) and Uruguay (Halty), as well as in Mexico (Santos Zetina) and other middle American states, the disease is well known, and cases have been reported from the Bahamas (Kinneard) and the Canaries (Darius Montesino).

In the United States venereal lymphogranuloma has been described in its various manifestations and under various names in such numbers of persons that the disease can no longer be considered rare. Reports have appeared not only from coastal cities and seaports, where there is a possibility of its importation in infected sailors (Wilmoth; Whitmore) but also from many inland cities. From the the eastern section of the United States cases have been reported from New York (Wise; Bloom; Elitzak and Kornblith; and Goldberger and Auslander), from New Jersey (Talbot; Silvers), from Pennsylvania (Martin, several series of case reports from 1933 to 1936; Beacon; Grossman), and from New England states (Howard and Strauss; Giffin). Cases have been reported from the Central states (Amtman and Pilot; Wien and Perlstein; Lash; Reichle and Connor; Dorne and Zakon; Lee and Staley; Dalton). The Southern states are practically all represented in the case reports—Arkansas (Goldstein and Byars), Oklahoma (Allen), Kentucky (Alley), Tennessee (Williams), Florida (A. Brown), Texas (Smith; Lehmann and Pipkin) and Louisiana (D'Aunoy, von Haam and Lichtenstein). In the Middle and Far Western states the disease seems to be rather uncommon, with case reports coming only from Nebraska (Tomlinson and Cameron), California (Templeton and Smith; Diepenbrock and co-workers; Novy) and Washington (Jones). From Canada only a few cases are reported (Desforges; Marin; Bourgouin). In additional cases in Alabama, Georgia, South Carolina, Virginia, Wisconsin and Michigan, although at present unreported, the disease was diagnosed with antigen furnished by us to interested physicians at various medical meetings. This brings the number of states in the United States in which venereal lymphogranuloma has occurred to 27, 11 of these states, or nearly 50 per cent, belonging to the Southern group.

More extensive statistics regarding the frequency of the disease in various large cities of the United States have been published by De Wolf and Van Cleve, S. H. Gray and co-workers, and D'Aunoy and von Haam. The Cleveland investigators published a report in 1932 of a series of 1,010 Frei tests made on patients hospitalized for various conditions; 58 of these gave positive reactions, and in every instance a positive history of venereal lymphogranuloma could be elicited. S. H. Gray and his co-workers, of St. Louis, tested a large number of patients coming to the city venereal clinic and obtained positive reactions in

40 per cent of the colored patients and in 3.4 per cent of the white patients. Using the same test as a routine on all colored patients applying to the outpatient dispensaries of the Charity Hospital of Louisiana at New Orleans, D'Aunoy and von Haam obtained positive results in 17.4 per cent. In most of the cases in which the Frei test was positive a definite history of the disease could be obtained. The same authors were able, during the period from May 1934 to May 1936, to observe 547 clinical cases of the disease in its various manifestations, and in an analysis of the records of 40 cases of elephantiasis of the vulva and 1,285 cases of rectal stricture, von Haam and Lichtenstein came to the conclusion that at least 20 per cent of the cases of elephantiasis and most of the cases of inflammatory stricture of the rectum observed in New Orleans from 1911 to 1935 could justifiably be suspected as cases of venereal lymphogranuloma.

From this brief résumé of the geographic distribution of venereal lymphogranuloma it can be concluded that the disease is an endemic infection of countries with warm or moderate climates. Regions of high altitude, such as the Rocky Mountain areas of the United States, the European Alps and the highlands of Tibet, do not have many cases, while low lands with considerable humidity, such as the Mississippi Valley, the coastal marshlands of Louisiana and the area about the Black Sea, seem favorable to the spread of the disease.

Racial Incidence.—It is generally stated by authors who have had opportunity to observe large numbers of cases of venereal lymphogranuloma that the Negro race seems more prone to contract the disease than the white race. Observations in North America are especially valuable in this respect because of the racial mixture of the patients frequenting the free clinics of the larger American cities. In Philadelphia, with a Negro population of practically 11 per cent, Bacon observed 31 cases in white persons and 118 in Negroes. In Indianapolis, according to Dalton, inguinal lymphogranuloma occurs as frequently in white persons as in Negroes. In Cincinnati 11 of the 16 cases of inflammatory stricture of the rectum observed by Lee and Staley concerned Negroes. In Cleveland De Wolf and Van Cleve saw twice as many Negro men as white men with inguinal buboes due to venereal lymphogranuloma, and Gray and his co-workers obtained positive Frei reactions in only 3.4 per cent of their white patients, while 40 per cent of their Negro patients had positive reactions. Our records demonstrate still better this racial difference in the incidence of venereal lymphogranuloma. Of our 547 patients, only 24 belonged to the white race. A satisfactory explanation of this peculiar racial incidence of venereal lymphogranuloma cannot be given at present. C. F. Martin discusses the possibility of a "fibroplastic diathesis" (Rosser) in the Negro race.

Stannus expressed the opinion that the manner of living and the loose moral code of Negroes may account for the preponderance of the disease in their race. Although racial constitution is no doubt an important factor in the distribution of many diseases, we are inclined to agree with Stannus that living conditions and loose social conditions are responsible for the wide occurrence of venereal lymphogranuloma in Negroes.

Sex Incidence.—As long as the various clinical manifestations and pathologic lesions of venereal lymphogranuloma were not fully known, the disease was believed to be restricted to the male sex (Hanschell; de Bellard). Only when it was proved that esthiomène of the vulva and inflammatory stricture of the rectum were manifestations of venereal lymphogranuloma was it realized that the disease occurred in women, although with different clinical and pathologic pictures. No doubt there is a preponderance of the disease in males, but this preponderance is not as marked as was maintained in the older literature. Gray and co-workers reported the same incidence of positive Frei reactions in men as in women. In our series of 547 patients 194 were females and 353 were males. In a series of routine Frei tests on 960 females and 509 males, we obtained 118 positive reactions in men and 79 in women. These figures perhaps represent more accurately the true sex incidence of the disease than do figures based on a single clinical manifestation of the disease (De Wolf and Van Cleve; Hellerström; Phylactos, and others). The explanation for this sex difference is purely hypothetic. Pautrier suggested that the virus of venereal lymphogranuloma may exist in the vagina as a harmless saprophyte. Coutts and Banderas Bianchi shared this opinion, although there is no experimental proof therefor. Much more plausible seems the explanation of Schulmann that in women the disease during the acute stage is mild and passes unnoticed or that the lesions are usually deep seated, hidden in the vagina (Naumann) and not readily recognized. L. A. Gray stressed the importance of chronic urethritis in women as a manifestation of venereal lymphogranuloma. Chevallier and Bernard observed a female patient in whom chronic periurethral edema was the only clinical evidence of infection. That the disease is transmitted from male to female and vice versa is proved in numerous so-called partner cases in which the history of infection can be traced to coitus or sexual perversity (Lévy-Franckel and Temerson; Chevallier and Moline; Nicolas and Lebeuf; Juvin; Hoffmann; Lépinay and Grévin). We are of the opinion that as knowldege of the various clinical forms of the disease progresses the difference in its sex incidence will be greatly reduced.

Age Incidence.—As with other venereal diseases, the largest incidence of venereal lymphogranuloma is in persons who are between the

twentieth and fortieth years of age—the period of greatest sexual activity. Seventy of our patients were between 14 and 20 years of age; 11 were over 50 years of age. Cases in children have been reported by Weiss and Cain, Chevallier and co-workers, Elitzak and Kornblith, and Luján and Rotter. In the case reported by Luján and Rotter, mere contact with infected adults was responsible for the infection. Since women suffer more from the chronic manifestations of the disease (esthiomène and inflammatory stricture of the rectum), female patients are of a higher average age than are male patients. All of our patients over 40 years of age were women.

The question whether venereal lymphogranuloma can be transmitted from parent to offspring has been discussed by Dick, who reported a case in which the apparently well child of infected parents had a positive Frei reaction and another case in which the apparently healthy newborn infant of a mother with rectal stricture had a positive Frei reaction. Since the diagnostic value of the Frei test at birth and in early childhood has been doubted because of the tenderness of the skin, we do not believe that Dick's findings are sufficient proof for his conclusions.

Occupational Incidence.—Venereal lymphogranuloma is reputed to be a disease of seaports, of the slum districts of larger cities, and of brothels and their devotees. Undoubtedly the afflicted patients belong to low social classes. We have observed but a single case in a person of high social standing. The female patients are usually prostitutes, a a class in which an incidence of as high as 10 to 15 per cent is reported. Schulmann and also Bejarano and Gallego Calatayud expressed the belief that at least 10 per cent of all prostitutes are infected. The largest group of white male patients is made up of sailors; so the disease is well known to naval medical officers. Philipps, Whitmore, Treibly and Wilmoth have described cases in the American Navy. Gibson stressed the importance of the disease for the English Navy, especially for the far eastern contingents. Hanschell as well as Müller and Justi noted that the engine room crews, exposed to hot and humid atmospheres, are more susceptible to the infection. C. F. Martin issued a stern warning concerning the rapid and uncontrolled increase of the disease among persons of the lower strata of society, stressing the financial burden which treatment of the disease in free clinics will bring to communities. He expressed a pessimistic outlook regarding the disease. Two years after recognition of venereal lymphogranuloma in New Orleans, it became necessary to open a special clinic for it. Here, from 10 to 12 new patients are seen each day. Additionally, the public hospital wards are filled with patients suffering hopelessly with inflammatory stricture of the rectum. Venereal lymphogranuloma is a disease which in our opinion threatens to become a grave public health problem in the United States, especially in its southern portion.

CLINICAL MANIFESTATIONS

Few diseases present such a variety of clinical symptoms and pathologic lesions as does venereal lymphogranuloma. Many of these seem so little related to each other that some authors still hesitate to attribute them to the action of a single etiologic agent. With the aid of Frei's intradermal reaction, we now believe, recognition of at least the principal manifestations of this venereal disease is possible. For better analysis of the symptom complex of venereal lymphogranuloma, it is deemed convenient to consider separately such symptoms as are related to the circumscribed genital and extragenital lesions and such as may be considered evidences of general invasion. Little is known concerning the evolution of the disease as a systemic complex, although much evidence can be adduced in favor of such an invasion actually occurring. In our clinical studies we were much impressed by the fact that the disease frequently consists not only of local manifestations but also of rather general systemic reactions.

Primary Lesions.—Various types of primary lesions may be encountered. Sézary and Drain described five types. The syphiloid, nodular and infiltrated types of primary lesions are seen rarely. They have been reported by a number of authors (Sézary, Bolgert and Joseph; Sézary and Perrault; Bory; Ravaut and Scheikevitch; Nicolas, Lebeuf and Rousset, and others). The most common type is a small herpes-like eruption, usually located near the coronal sulcus, neither tender nor suppurating and showing a tendency toward spontaneous healing. In the majority of cases this lesion is completely overlooked by the patient and has usually disappeared when he consults a doctor. In our series, 47 lesions of this type were seen in men and 2 in women; in both of the latter cases the lesion was located on the inside of the labia minora. The so-called lymphogranulomatous chancre is inclined to persist for some time, shows a rather deeply ulcerated area and is associated with more or less distinct lymphangitis, which can usually be traced to the swollen glands at the root of the penis. Sometimes, especially in patients with long or narrow prepuces, a nonspecific balanitis is present.

Indeed interesting are the reports of a primary lesion within the male or the female urethra with or without the formation of a small, well defined ulceration. A lesion at this site is supposedly more frequent in females. Gray reported 25 cases in which such a lesion resulted in urethral stricture. Curth, Frei and co-workers, Kalz, Polak and Bezecny have described similar cases, and Stannus considered a possible relationship between such lesions and the nonspecific types of urethritis described by Waelsch and more recently by Hissard and Husson.

Extragenital primary lesions have been ascribed to infection contracted while handling patients (Klotz; Phylactos; Hellerström; Homma and Chaglassian) or as a result of sexual perversities, such as cunnilingus or coitus in ano (Curth; Bezecny and Sagher; Buschke and Curth; Bloom; Wehrbein, Buschke, Boss and Vassarhelyi). Coutts described 12 cases in which there were diffuse swelling and thickening of the tongue—glossitis marginata—which he considered as a lesion of venereal lymphogranuloma contracted through cunnilingus.

Inguinal Bubo.—This must be regarded as the principal manifestation of the acute stage of venereal lymphogranuloma. It begins as a firm hard mass, not very painful and usually involving several groups of lymph nodes (von Haam and Lichtenstein). Within one or two weeks the glandular mass becomes attached to the skin and subcutaneous tissue, and fluctuation can be noted. It is at this stage that the patient complains of severe pain in the groin. Usually the skin now takes on a characteristic livid discoloration, which has led to the popular term "blue balls," and its shiny appearance predicts threatening rupture of the mass. Some buboes, however, never reach this stage, and involution of the firm masses without suppuration may be observed—the so-called abortive form of venereal lymphogranuloma. However, once the stage of fluctuation is established, suppuration with the formation of sinuses in the skin is unavoidable. Perforation of the bubo through the skin usually relieves the pain, and many patients carry such fistulous sinuses for many months without complaining of much discomfort. As a rule, numerous sinuses are formed, giving the inguinal region the appearance of the mouthpiece of a watering pot. This has caused Fiessinger to introduce the name "poradenitis." Healing of such a fistulous mass is usually slow, and the sinuses continue to drain pus for months, even years. The scars which later form in the inguinal region are callous and contracted and extremely characteristic of the disease.

The marked difference in the frequency of inguinal buboes in male and female patients suffering from the disease is sufficiently explained by the different anatomic distribution of the lymphatics in the sexes (Stannus). The lymphatics of the penis, the most common site of the primary lesion in males, drain to the superficial and deep inguinal glands; those of the deeper parts of the vagina or the cervix, the area which is probably the most common site of the primary infection in females, drain to the external iliac, retrocrural, hypogastric, pararectal and parasacral glands. Whether glandular disease similar to that observed in males occurs in females in the deeper seated glands, which are unavailable for inspection, or whether the acute infection in females takes a different course, is pure speculation at present. In our series, 278 inguinal buboes were observed in males and only 31 in females. These

figures coincide with those reported by other observers (Reiter; Gottlieb; Frei and Hoffmann). The majority of our patients (187 men and 20 women) had unilateral glandular buboes, a finding stressed by Ruge and Hellerström. The femoral and iliac glands are but rarely affected (Kitchevatz and Alcalay). If the primary lesion is extragenital, the regional glands undergo changes similar to those seen in inguinal bubo (Klotz; Coutts; Curth). Chevallier and Moline reported a case of conjugal infection between husband and wife, in which the woman had a swollen palatal gland, a feature seen otherwise only in von Mikulicz' disease. General adenopathy has been reported as a consequence of infection with the virus (Chevallier and Barreau) but is considered rare by Stannus. The principal clinical symptoms produced by these buboes are: pain, complained of in 52.9 per cent of our series; local tenderness, noted in 83.5 per cent; suppuration, present in 39.4 per cent.

Coutt's attempt to divide the disease, according to lymph gland involvement, into two different entities caused by virus A and virus B has met with severe criticism by Stannus. On the basis of our experience we are not able to accept Coutt's classification. Lymphangitis may accompany the bubo and has been reported by Coutts (thrombolymphangitis of the penis) and by Nicolau and Banciu. Several times we have observed swollen dorsal lymphatics of the penis. One case was noted in which suppuration was present in three distinct sections of such a lymph vessel. The disappearance of the inguinal bubo usually marks the end of the disease in the male, and in the majority of cases no serious sequelae result.

In contrast to the course of lymphogranuloma in males, in females the manifestations of the disease are frequently chronic—esthiomène and inflammatory stricture of the rectum.

Esthiomène; Elephantiasis of the Pudenda; Genitoanorectal Syndrome.—Since the report of Frei and Koppel in 1928 and of Koppel in 1929, numerous authors have proved beyond doubt that venereal lymphogranuloma is the cause of hypertrophic ulceration of the pudenda in most of the cases. Hellerström in 1934 listed over 200 cases of esthiomène, reported by 22 authors; 97.5 per cent of the patients had positive Frei reactions. Although more common in females, hypertrophic lesions can be observed also in males, involving the penis and the scrotal sac. In our series we have observed hypertrophic ulceration of the pudenda in 56 patients, 3 of whom were of the male sex. In 27 of the females the ulcerative process was more outstanding, while in 26 elephantiasis of the parts involved was dominant. There was no distinct correlation between the ulcerative and the hypertrophic changes as regards either location or duration. In some cases, the mucous membrane of the hypertrophied labia presented rather superficial and irregular ulcers; these were tender to touch and resisted all treatment. From 13 females a his-

tory of previous inguinal bubo could be elicited. The hypertrophic type of lesion shows at first only thickening of the affected parts, resembling chronic edema. The mucous membrane feels leathery and dry. With increase in size of the tissues, discoloration of the mucous membrane over the affected parts can be noted, with secretion of a thin cloudy fluid. Sometimes rather extensive superficial ulcerations appear and present all the usual signs of an acute pyogenic infection. As regards the distribution of the lesions and their extension, we may state from our observations that no definite rules are followed, the disease following a different course in each case, a fact which makes the clinical recognition of the condition difficult. In contrast to the inguinal bubo, however, we observed that involvement of parts of the pudenda was more often bilateral, with one side usually more severely affected. Five cases of isolated hypertrophy of the clitoris came under our observation.

Our 3 cases of esthiomène in males included, respectively, elephantiasis of the entire scrotum, elephantiasis of the left part of the scrotum and elephantiasis of the penis. In the case in which the condition was unilateral, complete extirpation of the glands of the affected side was followed for many months by a fistulous process within the wound before enlargement of the left side of the scrotum was noted. Similar cases have been described by others (Nicolau; Coutts and Martini Herrera; Navarro Martin; Louste, Cailliau and Schwartz). An interesting case in which the esthiomène apparently originated as a granulating tumor of the urethra has been described by Bezecny.

Secondary complications often bring serious consequences to patients suffering from hypertrophic lesions. Pyogenic infection and attacks of localized erysipelas are frequently observed in the tissues which have been deeply altered by the pathologic process. Carcinoma may develop on the basis of esthiomène, as in the cases observed by Bernstein and Philipp.

The principal complaints of patients suffering from hypertrophic lesions are local tenderness and an abundant secretion of exudate which soils the clothing. In some cases, however, no disagreeable consequences are felt, and the growth is permitted to reach fantastic dimensions.

The association of esthiomène with lesions involving the perineum, anus and rectum is reported with varying frequency in the literature. We have observed only 10 cases of this so-called genitoanorectal syndrome (Jersild); 7 of the patients were women and 3 were men. The exact evolution of this syndrome is still disputed, and while some authors believe that it is the result of retrograde spreading of specific lymphangitis (Stannus), Frei expressed the view that it represents actual infection of the subcutaneous tissue by the virus. Feilchenfeld maintained that in all cases of genitoanorectal lesions the primary lesion was in or around the anus, and Coutts claimed pederasty as its determining cause.

We have elicited a definite history of coitus in ano from 1 male and 4 female patients so affected. Kiefer observed the development of this syndrome after a furuncle-like primary lesion in the coccygeal region, and Ravaut, Levaditi and Maisler stressed its contagious nature by citing a partner case. Gougerot and Carteaud described the early appearance of the lesion as that of a small circumscribed nodule which soon becomes fistulous. Several such nodules appear, and the skin between them becomes edematous and hypertrophic. When fully developed, these lesions, as observed by us, show marked fibrosis and moderate hypertrophy of the perineum with numerous small sinuses and fistulas, extensive ulceration and always characteristic tags about the anus.

Inflammatory Stricture of the Rectum.—This lesion is without doubt the most serious manifestation of venereal lymphogranuloma. We have collected 97 cases. Of the patients, 90 were women and 7 were men; 5 (4 women and 1 man) were white, while the others were Negroes. Fifty-eight of our cases have been thoroughly analyzed and described (Lichtenstein). The clinical picture of the condition is rather uniform, and the history and the results of physical examination usually allow a correct diagnosis. The complaints are those of low grade obstruction with infection of the rectum and associated lesions of the anus and perirectal tissue. In prolongation of the condition cachexia, anemia and severe pellagra are noted. The rectal examination reveals in most instances an annular stricture 4 to 6 cm. above the anus, where it usually can be reached easily with the examining finger. The induration of the rectal wall is varying and in advanced cases produces such constriction of the lumen that the index finger will not be admitted. Thickening of the rectovaginal septum has been found in a great number of our cases and can be stressed as a valuable differential diagnostic sign. Below the stricture the mucous membrane of the rectum generally shows ulcerative and granulomatous proctitis, which makes examination extremely painful. The anal orifice is usually surrounded by large cauliflower-like excrescences. The most dreaded complication is the rectovaginal fistula, which was present in 14 per cent of our cases and which usually recurred after surgical repair. The fistulas which appear on the perineum sometimes heal spontaneously, only to recur as the disease progresses. C. F. Martin described the appearance of the diseased perirectal tissue and perineum as "rat bitten" and stressed the unyieldability and consequent undilatability of the stricture. He believed this condition to be worse than any manifestation of syphilis, "ranking very close to malignancy in its therapeutic aspects." Alley subdivided inflammatory stricture of the rectum into simple anorectitis, proctitis obliterans and fibrous stricture of the rectum. Sénèque described simple rectal strictures and strictures complicated with fistulas, with elephantiasis and

with pelvic cellulitis. Of the 11 patients dying with rectal stricture in the Charity Hospital at New Orleans during 1934-1935, 2 died of peritonitis caused by rupture of the stricture during dilatation and 4 following colostomy. The other 5 patients died with extreme cachexia, prostration and large decubital ulcers. Fifteen per cent of our patients with advanced stricture of the rectum showed typical pellagra. We concur in Martin's pessimistic prognosis regarding this manifestation of venereal lymphogranuloma.

Constitutional Symptoms and Remote Lesions.—More or less severe constitutional symptoms are rather characteristic of the acute stage of venereal lymphogranuloma, and they must be considered as important factors in the differential diagnosis. Rise in temperature occurred in over 50 per cent of our cases and has been stressed by others as a noteworthy sign in the differential diagnosis between venereal lymphogranuloma and soft chancre (Löhe and Blümmers; Guttentag; Buschke, Boss and Vasarhelyi). It usually precedes the appearance of the bubo and is accompanied by anorexia and prostration. Irregular temperature with chills indicates severe generalized virus infection. Headache was noted in over one third of our cases. Dizziness and slight nausea were usually present, as a rule forcing the patients to bed. Meningeal reaction with stiffness of the neck was observed by Nicolas and Lebeuf and by us, while Chevallier and Bernard reported what was possibly chronic meningitis in a woman suffering from the disease. Insomnia was stressed by Tran-Tan-Phat. Anorexia with occasional vomiting was present in 11 per cent of our cases, and Giacardy and Guttentag reported cases in which there was a resemblance to acute enteric infections. Loss of weight was prominent in 25 per cent of our series. One patient experienced a weight decrease of 30 pounds (13.5 Kg.) during the first week of the disease. Backaches were rather characteristic in our female patients, though rarely seen in men; this, we believe, can be taken as an indication that infection of the deeper pelvic glands is frequent in females. It is, as well, a constant symptom in patients suffering from stricture of the rectum and is sometimes associated with acute pelvic symptoms (Franchi). Various authors have recorded changes in the blood picture, although these are not believed to be characteristic (Nicolau; Stannus). Ravaut and Cachera found an increase of the mononuclear cells up to 17 per cent, and Ruge observed an increase in the total white cell count. The observation of mononucleosis was confirmed by others (Bernucci; Kristjansen; Gay Prieto). Chevallier and Bernard and Coutts and Banderas Bianchi found eosinophilia varying from 2 to 23 per cent. Coutts found that anemia is constantly present to a marked degree in what he terms the "second stage of the disease," an observation not made by Ruge or by us. Serologic changes have led to the introduction of various diagnostic methods, which will

be discussed in another chapter. The spinal fluid has been examined especially with reference to cephalalgia (Ravaut and Scheikevitch; Midana and Vercellino; Kitagawa). The hypertension of the spinal fluid observed by Kitagawa in 30 cases could not be found by Chaigneau, while the findings of Midana and Vercellino were refuted by Ravaut and Scheikevitch. Our examination of the spinal fluid in numerous cases did not show any deviation from the norm.

Remote lesions ascribed to venereal lymphogranuloma are being observed with increasing frequency, but caution in their evaluation is necessary in order to avoid erroneous conclusions. Short-lasting attacks of polyarthritis have been observed by a number of authors (Durand, Nicolas and Favre; Löhe and Blümmers), while others have reported true arthritis with exudative and chronic changes in the joint (Frauchiger; Caciro Carrasco; Koppel; H. Hoffmann; Gottlieb, and others). Coutts mentioned the similarity of the disease in such a form to gonorrheal arthritis and prepared a potent antigen from the exudate occurring in the joints. Severe involvement of joints, with sepsis was noted by Buschke, Boss and Vasarhelyi and by Reichle and Connor. Cutaneous lesions produced by the virus can be divided into two groups: general exanthems and local skin changes around or close to the genital lesions. Among the first, two types of erythema nodosum, multiforme and exudativum, have been described by numerous authors (Hellerström; Kleeberg; Frei and Hoffmann; Koppel; Chevallier and Bernard; Cuesta de la Almonacid; Gans; Kitchevatz; Buschke; Pinard and Fiehrer; Löhe and Blümmers). Representing the second group, small pustular or nodular lesions localized in the genital area have been observed (Pinard and Fiehrer; Cuestra de la Almonacid; Lévy-Franckel and Temerson; Sézary and Bardin; Chevallier and Bernard; D'Aunoy and von Haam). Stomatitis was observed by Gottlieb and by Löhe and Blümmers in their cases; conjunctivitis and episclerotitis, by Gottlieb, Hellerström and Koppel as well as by us in 2 instances. Eyeground changes—peripapillary edema of the retina and tortuosity of the vessels—were described by Kitagawa; the observation was confirmed by Coutts and considered by him as "highly specific" for the disease. Clinical suggestions that lesions occur also in the spleen and liver (Chevallier, Moricard and Lévy-Bruhl; Naumann; Pardo-Castello) and lungs (Hansmann) still require adequate confirmation.

It cannot be denied that the presence of constitutional symptoms and the occurrence of remote lesions during the course of venereal lymphogranuloma suggest a generalized systemic infection. However, considering the great rarity with which these remote lesions are encountered as contrasted with the frequency of the manifestations localized to the genital area, we believe that it can be assumed that in most instances disseminated virus is soon destroyed.

PATHOLOGY

In contrast to the rapidly increasing literature dealing with the clinical and statistical aspects of venereal lymphogranuloma, very little has been published recently concerning the pathologic changes initiated by the disease. The reason for this is twofold: first, most of the lesions are evanescent, and it is usually difficult to obtain biopsy material; second, many observers considered the histologic descriptions given before discovery of the Frei test as sufficient and needing no further elaboration. The material at our disposal has allowed us to study practically all of the pathologic changes described by various authors, and our numerous transmission experiments furnished rich material for the study of lesions produced by the virus in most species of animals. We shall now compare our observations with those recorded in the literature and attempt to trace the evolution of the disease from its primary lesion to its final stage.

Human Lesions.—We studied histologically two types of primary lesions—the lymphogranulomatous chancre and the herpetiform preputial lesion. The chancroidal form has a histologic appearance similar to that of a soft chancre of the Ducrey type. It consists essentially of necrosis of the epithelium and underlying connective tissue with abundant circumferential epithelial proliferation (von Haam). In the zone removed from the immediate region of necrosis and ulceration the lymph vessels are markedly dilated and filled with large endothelial cells. The herpetiform lesion is characterized by hyperplasia of the stratum granulosum with marked intraepithelial edema and dense infiltration of the entire rete Malpighii by small and large round cells and neutrophilic leukocytes.

The inguinal buboes have been so splendidly described by Durand, Nicolas and Favre that little can be added. The excised inguinal masses usually consist of a number of enlarged glands held firmly together by plastic periadenitis. In the early stage of the disease only a grayish, sometimes slightly hemorrhagic swelling of the glands is noted, but as the process advances the glandular tissue takes on a yellowish gelatinous appearance interspersed with small grayish white pinpoint areas. These are miliary abscesses. At this stage the periglandular tissue is usually markedly hemorrhagic and very edematous. The small focal abscesses enlarge, many become confluent, and finally pus breaks through the capsule of the gland, reaching the surface through numerous sinuses. If the patient is not treated surgically, these sinuses continue to form until the overlying skin appears as a sieve. The process has now reached its point of culmination and, with slow formation of a fibrous scar, healing follows, generally interrupted by frequent flare-ups resulting from pyogenic infections. Histologically the inguinal bubo of venereal

lymphogranuloma is especially characterized by proliferation of the endothelial cells lining the lymph spaces of the glands. Massing of large mononuclear cells occurs in the form of more or less circumscribed nodules—the *gommes lymphogranulomatosiques* of French authors. In some cases the disease remains arrested at this stage, with no actual destruction of tissue. In such cases firm, often indolent glands remain palpable for a long time, slowly undergoing resolution (formes frustes). In the majority of cases, however, invasion of the endothelial nodules by polymorphonuclear leukocytes takes place; the centers of the nodules become necrotic, and small abscesses surrounded by rather densely packed endothelial cells result. These abscesses usually assume a triangular or quadrangular shape (stellate abscesses) and diagnostically are quite characteristic. At the same time, fibrosis begins from the capsule of the node, a markedly vascular granulation tissue invaded by numerous plasma cells completely destroying the normal histologic structure of the gland. In chronic conditions no characteristic histologic glandular lesion can be noted. In the pus from inguinal buboes, as well as in the necrotic débris of the small stellate abscesses, small intracellular bodies were described by Gamna and Favre, who suggested that they represent inclusion bodies. Fischl, Todd and Bory confirmed the observation of such intracytoplasmic chromatophil bodies but expressed the opinion that they were phagocytosed cellular débris. Findlay, on the basis of careful study, classified them as nucleolar extrusions of the type frequently noted in other pathologic conditions. They are not identical with the small granulocorpuscles described by Miyagawa and his co-workers as corpuscular forms of the virus. We have seen similar structures, stained very irregularly with hematoxylin and eosin, in smears of pus and believe them to be nuclear débris resulting from necrobiosis.

Esthiomène and Inflammatory Stricture of the Rectum.—In their basic pathogenesis these chronic manifestations of venereal lymphogranuloma are identical, even though they occur in different anatomic structures; which develops depends largely on the location of the primarily infected lymph glands. Involvement of the inguinal, presymphysial or crural lymph nodes will affect the scrotum, penis or vulva, while infection of the anorectal, deep iliac and presacral glands will cause involvement of the perineum and of the lower part of the rectum. The essential pathologic process in both conditions is thrombendolymphangitis and perilymphangitis with a tendency to spread from the infected glands into the surrounding tissue. The changes in the lymph vessels are probably caused by direct action of the virus, as indicated by the experiments of Ravaut, Levaditi, Lambling and Cachera and of Löhe and Rosenfeld, and are not merely the effect of lymph stasis as Frei

believed. This chronic progressive lymphangitis accompanied by chronic edema and sclerosing fibrosis of the subcutaneous and submucous tissues results in induration and enlargement of the affected parts. The covering epithelium finally suffers from insufficient circulation, and ulceration occurs. These changes are observed earlier in the rectum, where the mucous membrane is more sensitive to changes in the submucous tissues, than in the skin of the perineum and genitalia. Pyogens invading such ulcerated areas play havoc in the altered tissue structures and establish foci of infection, ultimately responsible for the fast downhill course of patients afflicted with these lesions. The histologic picture of these chronic lesions is not characteristic and does not permit accurate diagnosis as conclusively as does the picture encountered in the acute bubo. Briefly summarized, the essential changes in rectal stricture are: destruction and ulceration of the mucosa; infiltration of the muscular layer by miliary accumulations of lymphocytes and plasma cells; dilatation of the lymphatics with perilymphatic infiltrations; thrombendolymphangitis (Barthels and Biberstein; Lichtenstein). Often the blood vessels show some endarteritic changes with narrowing of their lumens, which, however, is never as marked as in syphilis. The presence of specific granulation tissue comparable to the endothelial nodules in the lymph glands has been described in the chronic lesions by Gougerot and Carteaud, who observed *veritable gommes de Nicolas Favre* in very early lesions of elephantiasis of the genitalia and anus. These consisted of well circumscribed accumulations of neutrophilic leukocytes, eosinophils, mononuclear cells, plasma cells and epithelioid cells, showing at their centers homogeneous pink-staining material containing pyknotic and destroyed leukocytes and surrounded by dilated blood and lymph vessels, the latter usually filled with plasma cells. Barthels and Biberstein observed similar lesions in the ampulla of a rectum extirpated because of inflammatory stricture but thought that the gumma-like masses and small stellate abscesses were localized in the small lymph nodes and did not occur in the connective tissue. We have observed a case of elephantiasis of the vulva with numerous similar small gummas located beneath the mucous membrane. In these microscopic examination revealed large numbers of giant cells as noted by Babès in a similar case. Syphilis could be excluded. As frequent sequelae of rectal stricture, anal tags must be mentioned. Histologically these are composed entirely of dilated lymph vessels with perilymphatic inflammation. Lichtenstein suggested the name "lymphorroids" for these formations, which clinically are usually diagnosed as hemorrhoids. The sclerosing process extends far into the periproctal tissue, and the rectum has the appearance of being encased in cement. Numerous adhesions fix the lower part of the sigmoid and the rectum to the wall of the pelvis and to the neighboring organs, and in some cases a picture resembling that in chronic pelvic

inflammatory disease is produced. The histologic changes in the ulcerated mucous membrane are essentially those encountered in the ulcerations occurring in esthiomène of the pudenda. A primary disease of the rectal mucosa caused by the virus of venereal lymphogranuloma, so-called anoproctitis, which may give rise to rectal stricture, has been suggested by Coutts, who ascribed pederasty as its determining cause.

Extragenital Lesions.—Reports on the pathogenesis of extragenital lesions are rare, and much information is needed in order to draw accurate conclusions regarding widespread dissemination of the virus during the course of the disease. Gans described the histologic picture of a papular erythema observed in a patient with venereal lymphogranuloma. The lesion was strictly localized and consisted of only 10 to 15 papillae. The infiltrative leukocytic process was confined principally to areas around the blood vessels, in which the endothelial linings were swollen and desquamated. We observed a fistulous subacute epididymitis in a man with a strongly positive Frei reaction. The testis and epididymis were seeded with small stellate abscesses from which sinuses led to the skin of the scrotum. Microscopic examination showed a typical endothelial reaction with central necrosis and suppuration similar to that seen in lymph glands. D'Aunoy and Schenken observed venereal lymphogranuloma of the fallopian tube in a 20 year old Negress, who gave a history of pelvic pains with menstrual disturbance of six weeks' duration. A clinical diagnosis of chronic pelvic inflammatory disease was made and the patient treated by salpingectomy. Gross examination of the tube revealed a thickened, fibrous organ with partially obliterated fimbriate folds and whitish gray nodules in the region of the isthmus. Microscopic examination showed in the wall of the tube numerous stellate abscesses surrounded by typical masses of endothelial cells. The patient reacted positively to two Frei antigens. A very interesting case of localization of the virus in the human brain was observed by Schenken in this laboratory. A woman 45 years of age who had been suffering for some time with inflammatory stricture of the rectum was admitted to the hospital with symptoms of meningeal irritation. These were ascribed to pellagra, a frequent complication of stricture of the rectum. Autopsy and histologic examination revealed a diffuse meningeal reaction with lymphocyte and plasma cell infiltration and localized areas of superficial necrosis. Intracerebral inoculation of emulsions of this brain into white mice produced the typical picture of venereal lymphogranuloma encephalitis. The recovered virus was transmitted through several generations of white mice. Antigens prepared from these infected mouse brains gave positive cutaneous reactions in patients proved to have the disease. Lesions involving the urethra have been described in both males and females. We observed in each of 2 females a lesion of the urethra which transformed it into a rigid fibrous

tube. Biopsy showed granulation tissue with marked fibrous and lymphocytic infiltration. A Negro who came to the clinic of the State Charity Hospital of Louisiana at New Orleans because of swelling of the penis and difficulty in voiding was found to have a large granulomatous mass destroying the urethra. Microscopic examination of this mass revealed small nodules or bandlike arrangements of endothelial cells interspersed with polymorphonuclear leukocytes, lymphocytes and plasma cells. Giant cells resembling Langhans cells were present. Inoculation of guinea pigs with tissue emulsions produced no evidence of tuberculosis. The patient had a positive Frei reaction. Complete autopsies on patients with venereal lymphogranuloma have been reported by: Hillsman, Wilshusen and Zimmerman; Wernich; Wien and Perlstein; Wien, Perlstein and Neiman; Lichtenstein, Reichle and Connor. Most of the reports contain nothing of interest. In the case observed by Reichle and Connor, excision of inguinal buboes histologically characteristic of venereal lymphogranuloma was followed by purulent arthritis of the hip joint. At autopsy a large psoas abscess was found with destruction of the hip joint, as well as nodular masses in the kidneys and adrenals. On microscopic examination these masses showed "mononuclear abscesses" with central necrosis caused, in the opinion of the authors, by the virus of venereal lymphogranuloma. No attempts, however, were made to demonstrate the virus by animal inoculation, nor were diagnostic antigens prepared from the tissues. We have performed autopsies in 23 cases of chronic inflammatory stricture of the rectum and have not found such lesions as described by Reichle and Connor. The only notable observation which we wish to record from our autopsy experience is the occurrence of pellagra in 22 per cent of the cases of rectal stricture. As stated in previous publications, this coincidence is, to say the least, remarkable.

Lesions in Animals.—Lesions in animals have so far been observed only after experimental inoculation of the animals with the virus, spontaneous occurrence of venereal lymphogranuloma being unknown to veterinary medicine. Owing to the recent interest aroused by this disease, there are now available many accurate accounts of such experimental lesions in various susceptible animals.

Central Nervous System.—The best method of infecting animals with the virus of venereal granuloma is by intracerebral inoculation. The principal lesion so produced is encephalomeningitis, especially pronounced in certain types of monkeys, white mice and ferrets (D'Aunoy and von Haam) but infrequent in guinea pigs and rabbits. Macroscopically one observes moderate to marked diffuse hyperemia of the brain, not restricted to the area of trauma or its immediate vicinity (Miyagawa and co-workers). Microscopically the picture is that of

dense infiltration of the meninges of the brain, occasionally those of the upper part of the cord and the brain substance itself. Neutrophilic leukocytes, large and small mononuclear cells and plasma cells arranged in cell nests around the smaller vessels give rise to the so-called lymphomas. The choroid plexus shows similar areas of infiltration, and subependymal edema is often very characteristic during the acute stage of the disease. We have frequently observed pyknotic changes in some of the ganglion cells near the areas of infiltration, but in general the damage to nerve tissue proper is slight. The histologic picture is fairly characteristic, and the lesions can be easily differentiated from those of spontaneous encephalitis, described as occurring in various animals, especially white mice. Ionesco-Mihaiesti and co-workers described, after intraperitoneal inoculations, degenerative lesions in the columns of Goll with demyelination of axis-cylinders and glial proliferation similar to the histologic changes in human tabes. We have never seen such lesions, nor had Findlay. We believe with Levaditi and his co-workers that they resulted from spontaneous disease in the animals and were not produced by the virus. Levaditi designated the experimental lesions of the brain caused by the virus as "neuromesodermoses," in contrast to the neuroectodermoses produced by neurotropic viruses. Findlay produced lesions in the brain by intraperitoneal injection of the virus and simultaneous traumatization of the brain.

Skin and Lymph Glands.—The second most commonly used method of infecting experimental animals is the intracutaneous or subcutaneous inoculation of material containing the virus. This method is especially useful with respect to monkeys, guinea pigs and rabbits. The lesion produced at the site of inoculation is quite similar to the primary lesion seen in man. Findlay described it as a thickening of the epithelial layer with dense subepithelial infiltrations of few neutrophils and many plasma and plasmacytoid cells. The endothelium of the subepithelial capillaries is swollen to such an extent that the lumens are almost closed. Levaditi and Nicolas observed similar changes. The regional inguinal glands after such inoculations show lesions comparable to the inguinal buboes of the human disease. This is especially so in the guinea pig. With monkeys, however, such infections are followed by early and extensive abscess formation (Findlay). De Blasio, by direct intraglandular inoculation of infected material, produced similar lesions in the cervical glands of guinea pigs, and Bonne and his co-workers in Netherland East Indies noted similar changes following injection of material from climatic buboes.

Changes in Other Organs.—Caminopetros and Photakis obtained marked hyperplasia of the reticuloendothelial cells in the lungs of rabbits by intrapulmonary injection of the virus. Such lesions have been simi-

larly produced in rabbits and guinea pigs (von Haam and Hartwell). Macroscopically the lungs show small grayish areas resembling atelectatic lung tissue. Microscopically there is marked accumulation of endothelial cells with round cell infiltration. A single injection will eventually produce numerous such focal lesions throughout the lung. Meyer and co-workers noted perivascular changes in the liver after intrahepatic injection of virus-containing material. Splenic enlargement usually follows injection of the virus by any route (Meyer, Rosenfeld and Anders; Nicolas; de Blasio; D'Aunoy and von Haam). Subsequent to intracerebral inoculation Levaditi, Hellerström and Wassén and Findlay were able to recover the virus from the spleen. Miyagawa and his co-workers, by intratesticular injection of virus-containing material into white mice, produced in a few cases adhesions between the tunica vaginalis and the parenchyma of the testicles with atrophic and sometimes purulent changes. Intraperitoneal inoculation causes adhesive peritonitis (Ionesco-Mihaiesti and co-workers). Corneal scarification in monkeys did not produce keratitis, but injection of virus-containing material into the vitreous produced iridocyclitis with subsequent atrophy of the eyeball (Stannus). Intracerebral injection of material containing the virus into white mice, monkeys, ferrets, cats, sheep and calves produced in the majority of cases severe unilateral or bilateral conjunctivitis within from three days to two weeks (von Haam and Hartwell). Microscopically such lesions show hypersecretion of mucus by the columnar cell epithelium and infiltration by large and small mononuclear cells and sparse neutrophilic leukocytes within the subepithelial layer. Inclusion bodies have never been observed. The dissemination of the virus in animals infected experimentally is apparently dependent on the route of inoculation, intracerebral and intraperitoneal injections usually leading to general spread, while subcutaneous injection seldom produces more than a primary lesion and regional glandular swelling. The close identity of some of the lesions in animals with the lesions observed in man must be emphasized, suggesting the possibility of many yet undescribed lesions occurring in man.

ETIOLOGY

Numerous attempts have been made to cultivate the causal agent of venereal lymphogranuloma from the pus of "climatic buboes" or the buboes of "Nicolas Favre's disease." Through such efforts various types of organisms have been isolated by many investigators, although others consistently have found pus from such lesions sterile. As previously noted, most authors of the nineteenth century considered venereal lymphogranuloma as a tuberculous or syphilitic process, and some even ascribed its manifestations to Plasmodium malariae, Pasteurella pestis, fungi, diphtheroids, various types of cocci, amebas, unknown toxins,

constitutional factors and climatic influences (L. Martin; Cantlie; Ruge). The greatest difficulties under which investigators of this period worked were undoubtedly inability to select cases in which there were no complications and inability to reproduce the disease in experimental animals. These handicaps were removed by the discovery of the specific skin reaction by Frei, in 1925, and the transmission of the disease to monkeys by Hellerström and Wassén, in 1930. Shortly thereafter, these Swedish workers, as well as Levaditi, Ravaut, Lépine and Schoen, demonstrated a filtrable virus as the causal agent of the disease. In the United States Grace and Suskind and D'Aunoy, von Haam and Lichtenstein demonstrated the presence of the virus as an endemic infectious agent in New York and New Orleans, and D'Aunoy and his co-workers established the identity of their strains with the virus isolated by continental workers. Since its discovery, the presence of the virus in cases of venereal lymphogranuloma has been confirmed by authors all over the world, and the etiologic significance of the virus is now well established. According to McKinley's classification, it belongs to the group of filtrable viruses without cell inclusions.

Habitat and Routes of Infection.—The virus of venereal lymphogranuloma has been recovered from the tissues and exudates of the primary lesion (Löhe, Rosenfeld, Schlossberger and Krumeich); from the pus and tissues of inguinal buboes (Hellerström and Wassén; Levaditi and co-workers; Findlay; Cohn and Kleeberg; Freund and Reiss; de Blasio; Nicolau; Caminopetros, Phylactos and Photakis; Grace and Suskind; von Haam and Lichtenstein; Bizzozero and Midana; Miyagawa and co-workers, and others); from the tissues of the chronic lesions—esthiomène and inflammatory stricture of the rectum (Ravaut and co-workers; Laederich, Levaditi, Mamou and Beauchesne; Levaditi, Mollaret and Reinié), and from the spinal fluid of patients with the disease in acute form (D'Aunoy and von Haam). Transmission of the disease by means of the blood (Findlay; von Haam and D'Aunoy) or the saliva (D'Aunoy and von Haam) of patients afflicted with the disease has not been possible. In none of the reported cases of remote extragenital lesions, such as cutaneous manifestations or arthritis, has the virus been proved by animal inoculation to have been directly responsible. Coutts's theory that the virus is of buccal origin is based purely on clinical evidence (Coutts; Coutts and Banderas Bianchi). A carrier state has never been demonstrated in healthy human beings.

In most cases the genital tract is the portal of entry for the virus in man. The virus is probably transmitted through direct contact with the diseased mucous membrane during coitus, numerous partner cases proving the venereal nature of the infection. Because of the evanescent character of the primary lesion in the female, this sex must be held

responsible for the greater number of cases of venereal lymphogranuloma in man. Simple contact, without sexual relations, may transmit the virus to children, as in the case reported by Luján and Rotter. Infected douche instruments have been blamed for transmission of the virus among women. The question of an intermediary animal host which may play a role in the transmission of the virus has been raised by Coutts, and he incriminated the pubic louse, met so often in patients of the low social stratum affected by venereal lymphogranuloma. So far no proof sustaining his contention has been adduced. We have unsuccessfully searched for concurrence of venereal lymphogranuloma and pediculosis pubis. Sexual perversions may produce extragenital infection, and careless handling of infectious material may bring the disease to physicians and nurses. Bonne, van der Horst and Pet reported in 1933 that diagnostic antigen prepared according to the method of Frei produced in 3 volunteers one to six weeks after inoculation typical axillary buboes, and they argued that the temperature recommended by Frei may not kill all "strains" of the virus. We have had a similar experience. A batch of heated mouse antigen produced typical axillary buboes and small pustular lesions at the site of injection. We ascribed this to carelessness in the preparation of the antigen rather than to unusual resistance to heat on the part of the virus used. Purposeful infection of human beings has been reported (Levaditi, Marie and Lépine; Levaditi, Ravaut and Cachera; Chevallier and Bernard). Only in the case reported by Levaditi and co-workers was a regional bubo produced.

The period of incubation varies between three days and three weeks. We encountered a case in which a primary penile lesion appeared two days after intercourse and another in which buboes appeared as late as four weeks after coitus. An interval of about one week usually elapses between the appearance of the primary lesion and the establishment of the inguinal bubo. One of our female patients received a slight laceration during intercourse, and an inguinal bubo developed three days later. The frequent absence of any discernible primary lesion makes accurate determination of the period of incubation extremely difficult.

PHYSICAL CHARACTERISTICS OF THE VIRUS

Filtrability and Size.—That the virus can be filtered through the usual bacterial filters has been definitely established by Hellerström and Wassén and Levaditi and his school, but filtration is not successful in every instance. This is not surprising in view of the many factors involved, such as the hydrogen ion concentration and nature of the virus emulsion, the preparation and electrical charge of the filter, the absorption of virus, etc. According to Findlay, the virus can be filtered better from emulsions of monkey brains than from emulsions of mouse brains.

We have succeeded in passing the virus in emulsions of glands from infected monkeys, mice and ferrets and from the membranes of infected eggs through Chamberlain candles L3. We have failed, however, to recover the virus from filtered pus of inguinal buboes. Miyagawa and co-workers succeeded in passing the virus with ease through such filters as Chamberlain L2 and L3, Berkefeld V and N and Seitz E. K. They also passed the virus through collodion membranes with pores smaller than 0.24 micron. Our recent experiments have shown that purification of virus suspensions by the isoelectric point method facilitates their filtration (D'Aunoy and Andes). Broom and Findlay estimated the size of the virus to be between 0.125 and 0.175 micron, similar to the size of the virus of vaccinia. Visible forms of the virus were described by Miyagawa and his co-workers. In smear preparations from human infected glands and from lesions in the central nervous systems of experimentally infected animals, they found spherical microcorpuscles, approximately 0.3 microns in diameter. They regard these not as identical with the Gamna bodies but as corpuscular forms of the virus, their minute size allowing passage through collodion, Seitz and other filters. We have not been able to confirm the observations of these Japanese authors.

Resistance to Physical and Chemical Agents.—The virus shows little resistance to heat, being inactivated when exposed to 56 C. for thirty minutes, according to Levaditi, Marie and Lépine, or for ten minutes, according to Miyagawa and co-workers. The same authors observed that it remained virulent for twenty-three days at temperatures of 4 C. and for thirty days in a frozen state. Hellerström and Wassén obtained practically similar results. According to Findlay, freezing and drying in vacuo preserve material containing the virus without loss of virulence for three months. We have desiccated infected ferret brains in vacuo at freezing temperature, stored them in the ice box (4 C.) for twenty-five days and found them still infectious for white mice. Solution of formaldehyde U. S. P. in the concentration of 1:1,000 renders the virus inactive, while phenol and sodium ricinoleate in the same concentration have only an attenuating effect on it, mice inoculated with virus suspensions so treated dying sixty to ninety days after inoculation. In contrast to the neurotropic viruses, the virus of venereal lymphogranuloma is quickly inactivated by glycerin (Levaditi and co-workers). In the presence of oxygen and light methylthionine chloride (methylene blue) and acriflavine in concentrations of 1:100,000 inactivate emulsions of virus-containing mouse brain; in the absence of light these dyes in similar concentrations have no such effect. The action of ultraviolet rays and radium has been studied by Levaditi and by Levaditi and Reinié, who found that exposure of emulsions of virus-containing matter

to the rays of a mercury vapor lamp for thirty minutes rendered them noninfectious, while exposure to the gamma rays of 7.5 millicuries of radium did not affect their virulence.

BIOLOGIC CHARACTERISTICS OF THE VIRUS

Natural and Acquired Immunity.—The problems of immunity are practically open chapters in the knowledge of venereal lymphogranuloma. Whether natural immunity to the disease occurs in man is still undecided. The marked prevalence of the disease among Negroes we attribute, in accord with other authors (C. F. Martin and others), more to the unhygienic and unsocial methods of living among them than to greater racial susceptibility. The question of permanent immunity produced by the disease or by subclinical infections with the virus is still undecided. We are of the opinion that cases of reinfection (Kitchevatz) can be explained as simple recurrences resulting from residual infection.

Antibody Production.—Without doubt, the appearance of specific sensitivity to Frei's antigen indicates the production of specific antibodies in human and animal hosts. The nature of these antibodies and their mode of action, however, have not been determined. Patients in the last stage of inflammatory stricture of the rectum react to the specific antigen in exactly the same manner as do patients with a slight or severe attack of inguinal bubo. This allergic condition persists for many years after the disease has apparently been cured and is only slightly influenced by such circumstances as old age, stage of nutrition, concurrent disease or reappearance of the disease (Nicolas, Lebeuf and Charpy). The presence of virucidal substances in the serum of patients recovering from venereal lymphogranuloma is reported by Levaditi, Ravaut, Lépine and Cachera and confirmed by Findlay. Working with guinea pigs and monkeys, Miyagawa and co-workers were also able to demonstrate virucidal substances in human convalescent serum. In our experiments serum from patients convalescing from acute inguinal buboes two to four months after infection did not neutralize emulsions of virulent mouse brains. Kalz and Sagher noticed milder evolution of the disease in patients administered serum from those convalescing from the disease. Gottlieb reported that Frei antigens are neutralized when mixed with convalescent serum and kept at ice box temperature for forty-eight hours. Gottlieb's results have not been confirmed by Miyagawa and co-workers, Gallego Calatayud or ourselves.

Plurality of Virus Strains.—The question of a plurality of virus strains in this disease is as yet undecided. Coutts concluded from his clinical studies that there are two different types of the virus, each producing various syndromes of the disease. Virus A, according to Coutts, is the etiologic factor of a strictly localized disease, "lympho-

granulomatosis venerea," while virus B produces a systemic infection of the lymphatic system, "lymphopathia lymphogranulomatosa." We have not been able in our extensive studies to find differences in the virus as isolated from various sources which would warrant such a belief. We admit, however, in agreement with Chevallier and Bernard, that we have found differences in aggressiveness and in invasiveness in the virus as variously isolated.

Animal Susceptibility.—After numerous failures and doubtful results Hellerström and Wassén reported at the session of the Eighth International Congress of Dermatology, in 1930, that they had succeeded in transmitting the disease to Macacus rhesus and Macacus cynomolgus by intracerebral injections of pus obtained from buboes of patients. Since this fundamental work numerous reports recording susceptibility of various animals to the virus have appeared. The following species of animals have been studied in regard to susceptibility: monkeys (de Bellard; Hellerström and Wassén; Levaditi and co-workers; Cohn and Kleeberg; Löhe, Rosenfeld, Schlossberger and Krumeich; Caminopetros, Phylactos and Photakis; Ionesco-Mihaiesti and co-workers; Findlay; D'Aunoy, von Haam and Lichtenstein; Grace and Suskind; Miyagawa and co-workers); rabbits (Chevallier, Lévy-Bruhl and Moricard; Freund and Reiss; Levaditi and co-workers; Caminopetros, Phylactos and Photakis; Findlay); guinea pigs (Ravaut, Boulin and Rabeau; Gay Prieto; de Blasio; Meyer, Rosenfeld and Anders; Freund and Reiss; Nicolau; Caminopetros, Phylactos and Photakis; Findlay; D'Aunoy, von Haam and Lichtenstein; Bizzozero and Midana); dogs (Nicolau; Findlay); cats (Levaditi, Ravaut, Schoen and Vaisman; von Haam and Hartwell); white rats (Findlay); field voles (Findlay); ground squirrels (Caminopetros and co-workers); ferrets, sheep, calves and frogs (D'Aunoy and von Haam). Of these, white mice, certain species of monkeys (M. cynomolgus, Hapale penicillata and the baboon) and ferrets are highly susceptible to the virus, a large percentage of these animals succumbing to its effects. Only a small percentage of dogs, cats and guinea pigs can be infected, while inoculation of rabbits, sheep and calves produces infection in rare instances. Chickens, ground squirrels and field voles may harbor the virus for ten to thirty days without presenting any symptoms or lesions, and in frogs and white rats the virus is quickly destroyed and does not affect the animals.

Passage of the virus from animal to animal is possible, the "Kamm" strain having been preserved in Levaditi's laboratory for over five years. In our laboratory, we have kept six strains highly virulent by biweekly transfer to new animals for four years. Repeated passage through the same species of animal may lead to increased invasiveness (Grace and Suskind) or in rare instances to autosterilization of the virus strain

(Levaditi). Passage from one species to another has been performed without difficulty, and passage from animal back to man has been successful (Levaditi, Ravaut, Lépine and Schoen). The type of lesion produced experimentally in the susceptible animal depends on the portal of entry of the virus. The most effective route of infection is the intracerebral one, wherein it is of little importance whether the inoculum be deposited subdurally or intracerebrally. The essential pathologic condition produced thereby is meningoencephalitis, which proves fatal to the majority of animals. General spread of the virus throughout the body following intracerebral inoculation has been proved to occur by Levaditi and Reinié. It was recovered from other organs after intracerebral infection of the animals by Levaditi, Ravaut, Lépine and Schoen and by D'Aunoy and von Haam. Meningoencephalitis can also be produced by intraperitoneal inoculation of the virus if the brain is simultaneously traumatized by injection of a sterile starch emulsion (Findlay). Bilateral fibrinopurulent conjunctivitis has been encountered with such regularity in intracerebrally infected animals that it must be regarded as significant (von Haam and Hartwell). Subcutaneous inoculation of the virus in monkeys, dogs, rabbits and especially guinea pigs produces at the site of injection a small papular lesion, with swelling of the regional glands, in about 30 per cent of cases. Occasionally generalized infection may follow such an injection (Meyer, Rosenfeld and Anders; Nicolau). Intraperitoneal inoculation (Mihaiesti and co-workers) may produce severe adhesive peritonitis. Intrapulmonary inoculation, according to Caminopetros and Photakis, produces characteristic lesions of the lungs in rabbits. Intravenous, intraocular, intraarticular and intranasal inoculations fail to establish the disease (Levaditi and Reinié). From emulsions of the organs of infected and diseased animals, potent antigens which can be used successfully for the Frei diagnostic reaction in human beings can be prepared (D'Aunoy, von Haam and Lichtenstein).

Cultivation of the Virus.—Successful cultivation of the virus in vitro was reported by Tamura, who claimed to have grown it by Maitland's method. The fluid portion of his cultures when heated served, he found, as excellent antigens for Frei's specific diagnostic reaction. Applying Tamura's method, we placed 0.1 cc. amounts of 20 per cent emulsions of infected mouse brains in Maitland tubes. Two to three days after inoculation a distinct cloudiness appeared in the tubes. From the second and third subcultures mice were inoculated intracerebrally with 0.1 cc. amounts of the supernatant fluid. In these mice characteristic histologic changes developed. We do not believe that this evidences virus growth. The dilution affected by subculturing was still well within the limits within which the material could prove infectious. Recent reports by Voet and by Miyagawa and co-workers fail to confirm Tamura's results.

Cultivation of the virus in the chorioallantoic membranes of hatching chick embryos was reported by Miyagawa and associates. These workers, employing the technic described by Goodpasture, Woodruff and Buddingh, were able to propagate the virus for five generations. Smears from the white plaques observed on the membranes after inoculation contained granulocorpuscles similar to those previously described by Miyagawa in human material. We have carried on similar experiments during the past two years and have been able to propagate the virus on the chorioallantoic membrane. We were unable to find specific histologic changes that could be ascribed to virus action, and interpreted the "bodies" described by Miyagawa as products of cell degeneration resulting from nutritional changes occurring during the normal development of the chorioallantoic membrane, which, it should be remembered, is an organ of excretion and respiration in the developing chick (D'Aunoy and Evans).

DIAGNOSIS

In general it may be said that the diagnosis of a disease can be made by four different methods: clinical methods, by which the manifestations and symptoms are observed and interpreted; bacteriologic methods, by which the causal agent is demonstrated; pathologicoanatomic or histologic methods, by which the tissue changes are evaluated and interpreted, and immunologic methods, by which the host's reaction to the noxious agent is elicited.

The diagnosis of venereal lymphogranuloma by purely clinical methods is possible in many cases but in our opinion is always difficult. In most cases a definite diagnosis cannot be reached by such methods alone. We have already discussed the principles underlying the clinical, bacteriologic and histologic diagnosis in the chapters dealing with the manifestations of the disease, the causal agent and the pathologic picture. In this chapter, therefore, we shall refer only to the immunologic diagnosis of venereal lymphogranuloma, discussing especially the technic and the diagnostic value of the Frei intracutaneous reaction.

Technic of the Frei Test.—Frei recommended, as proper material for the preparation of diagnostic antigen, bacterially sterile pus aspirated from the bubo of a patient suffering from venereal lymphogranuloma. This pus he mixed with four to six parts of physiologic solution of sodium chloride and inactivated the emulsion at 60 C. for two hours one day and for one hour the next day. Only after bacteriologic tests showed the material to be sterile did he consider it fit for use. Dind and Hellerström and Wassén made use of extracts of glands extirpated from patients with venereal lymphogranuloma under aseptic precautions. With these they obtained results that were as good as those obtained with emulsions of pus. In 1931, after Hellerström and Wassén had

isolated the virus of venereal lymphogranuloma, the former prepared emulsions of brain substance from monkeys suffering from meningoencephalitis following intracerebral injection of gland material from a patient with venereal lymphogranuloma. Such emulsions gave positive intracutaneous reactions in patients who had venereal lymphogranuloma and negative results in controls. Later Findlay and Wassén independently recommended the white mouse as the most practical animal for the preparation of antigen. Bloom, Kleeberg, and Grace and Suskind also recommended such antigenic material, the latter emphasizing that brain emulsions desiccated in vacuo at freezing temperature constituted by far the best material for use in the diagnostic skin test.

Although both types of human antigen proved generally satisfactory, we found difficulty in standardizing various batches of antigen prepared from material secured from different patients. Pus obtained from some patients possessed much weaker antigenic properties than that from others. We therefore adopted emulsions of brains from animals experimentally infected with the disease as standard antigen, and the use of this antigen prepared as a routine in our laboratories has proved the method of choice in obtaining acceptable results over a long period. While numerous animals are susceptible to the disease, only infected monkeys (common marmoset or Hepale penicillata) and white mice have proved useful as sources of brains for antigenic brain emulsions.

Since our clinical experiences suggested the possibility of virus strains of various aggressiveness (Chevallier and Bernard), we chose from 40 strains carried in our laboratories for from four to twenty-six animal passages the 6 which produced the strongest reactions in animals for use in the production of antigen. These 6 strains have been carried through mice by biweekly intracerebral injections and have remained unchanged in power of invasiveness for these animals. The inoculated dose is such that at the end of two weeks the infected animals show signs of sickness with marked histologic changes in the brain and meninges, but only few die.

The preparation of antigen from the brains of these animals follows the general outline published by Frei and by Hellerström:

A 10 per cent emulsion of brain in saline solution is heated to 52-54 C. for two hours the first day and for one hour the second day. Five tenths per cent phenol is used as a preservative, and tests for sterility are performed repeatedly in order to avoid using infected material. Antigens prepared from the various strains are pooled, the stock mixture containing all 6 strains. Stock antigen is kept in the ice box (4 C.) in the dark and the "date of expiration" set empirically at six months. Samples of older batches are always available for control tests. Before being used for diagnostic purposes, each batch of mixed stock antigen is tested for specificity and sensitivity. At least six tests on persons known to have venereal lymphogranuloma and six control tests on patients not infected are performed

and the results compared with those obtained with other stock antigen mixtures and human antigens.

By these means we have succeeded in obtaining antigen of high specificity and sensitivity which always produces the same type of reaction when tested on the same patients under similar conditions. It is our belief that the inactivating temperature of 60 C. recommended by Frei in the preparation of the antigen is too high and does not result in production of the best diagnostic antigen, judged by the criteria of specificity and sensitivity.

The technic which we employ for the Frei test follows in general the directions given by Frei:

After the forearm has been cleansed with alcohol, 0.1 cc. of the antigen is injected intradermally through a fine needle. This produces a small weal from 3 to 5 mm. in diameter. On the same arm the same quantity of an emulsion of normal brain from healthy white mice, which has been prepared and treated in the same manner and is of the same age as the antigenic emulsion, is similarly injected as a control. (The use of an emulsion of healthy mouse brain as the control for the antigen prepared from infected mouse brain is absolutely necessary and preferable to the injection of any other control material.) The reaction is read after forty-eight hours and reported as doubtful, positive, strongly positive or negative. A doubtful reaction is not regarded as diagnostic, and the test is repeated. If possible, a second reading is made on all reactions after four days. The site of the control injection at the time of the reading of the reaction usually shows only the mark of the needle with sometimes a small deposit of unabsorbed material. The positive reaction consists of an elevated and inflamed weal measuring 0.7 to 1 cm. in diameter. The strongly positive reaction shows a red edematous area measuring several centimeters in diameter and usually containing centrally placed small yellowish areas of necrosis. The positive reaction is discernible for several days and in some instances heals with distinct pigmentation at the area of injection.

Histologic examination of tissue obtained from the site of a positive Frei reaction shows marked hyperemia with vascular dilatation and perivascular accumulation of lymphocytes and plasma cells but comparatively few neutrophils. The epithelium shows some edema but otherwise not much damage. Only in very severe reactions is there necrosis of the epithelium and of the subepithelial structures. We have not been able to demonstrate inclusion bodies or bacteria in these lesions. Sézary, Lévy-Coblentz, Mauric and Lenègre described an identical picture and emphasized the close similarity to the histologic picture of the Dmelcos reaction for infection with Ducrey's bacillus.

The Diagnostic Value of the Frei Reaction.—The introduction of the specific skin test by Frei in 1925 can rightly be hailed as a "milestone of great importance" (Stannus) in the diagnosis of venereal lymphogranuloma. It stimulated tremendously further studies of the disease. With the aid of this test, the etiologic relationship between venereal

lymphogranuloma and climatic bubo (Findlay), inflammatory stricture of the rectum (Frei and Koppel) and nonspecific urethritis of the Waelsch type (Frei, Wiese and Klestadt) was demonstrated and the complete clinical entity of this virus disease ultimately established. Since the condition of allergy which is the cause of the positive reaction of the skin remains for many years after healing of the lesions—perhaps even throughout the life of the patient—a positive reaction does not indicate the presence of active disease and has perhaps less differential diagnostic value than a negative reaction, which definitely excludes the infection, active or latent. This fact must be borne in mind, especially if a positive reaction is obtained in an older person. In such a case the possibility of a previous infection with venereal lymphogranuloma should always be excluded by careful consideration of the past history. On the other hand, some time elapses after infection before the specific allergic state of the host is reached; therefore the false negative reaction is encountered frequently, particularly in patients with the infection in a very acute stage and in those in whom allergic responses are slow. These factors explain the majority of discrepancies which have been reported between the clinical findings and the results of the Frei test (Gaté and co-workers). Careful evaluation of the clinical history and repetition of the test after a lapse of some time will clear most such apparent discrepancies and considerably increase the diagnostic value of the Frei test.

Many investigators (Frei and his school; Hellerström; Hermans; Jersild; Löhe and Blümmers, and others) have confirmed the specificity of this test in numerous cases of the disease. Frei, Wiese and Klestadt emphasized the importance of the proper selection of the case in which to obtain the material from which the antigen is prepared, and his careful criticism of all reports in which doubt had been expressed as to the specificity of the reaction bearing his name brings out several important points, such as coexistent venereal infections and faulty preparation of the antigen.

The antigen must be prepared from material obtained from a patient with the disease in a typical form, and its bacterial sterility should be tested repeatedly. Control tests should always be made in order to exclude false positive reactions resulting from general skin hypersensitivity. The material used for control tests must be homologous to the specific antigen. If emulsions of brains of infected animals are used, it is essential that emulsions of normal homologous brains be used for control injection in order to avoid false positive reactions due to the sensitivity of the skin to the brain substance of the animal (von Haam and Hartwell).

Our results with the Frei test have been most satisfactory. Tests performed on over 500 patients with clinical venereal lymphogranuloma

and over 800 controls who did not have this disease gave 98.1 per cent correct results. Of the positive reactions, only 7.2 per cent were "weakly positive" (D'Aunoy and von Haam). After distributing portions of our standard mouse antigen to interested physicians in various parts of the country, we obtained from 90 per cent of these physicians reports of results in complete agreement with clinical findings. These results are in accord with the observations of Flandin, Rabeau and Turiaf, who reported 1,170 Frei reactions on 400 patients with 95 per cent correct results. Smaller series published by others (Dalton; Curth; Cole; Grace and Suskind; Vander Veer and co-workers) gave 100 per cent correct results. An extensive review of the evidence for the diagnostic value of the Frei test, presenting statistics from 41 other clinics, was reported to the American Proctologic Society by Bacon, of Philadelphia. Only 6 of the various contributing authors reported satisfactory results in less than 90 per cent of their cases, the most unsatisfactory results being in cases of rectal stricture. Repeated Frei tests in patients with venereal lymphogranuloma observed for two years demonstrate, according to Bacon, that one negative test should not be considered as sufficient evidence to exclude venereal lymphogranuloma if the clinical evidence speaks for its presence.

Simon, Braley and Minck applied the Frei test to 50 female patients picked at random and obtained 12 per cent positive results; only a single patient showed an esthiomène-like lesion on the vulva which could be considered clinically as evidence of infection with the virus. Their conclusion that the Frei reaction gives erroneous results in 10 per cent of patients tested is sharply criticized by Sézary and Lenègre, who point to the possibility of latent or veiled infections, especially in females. Weiss and Kuntzmann reported a series of cases in which histologic observations bore out all positive Frei reactions. We have had similar experience in all cases in which patients with positive Frei reactions were operated on. Levaditi, Durel and Reinié observed differences in the strength of antigens prepared from emulsions of brains of different monkeys. We have made similar observations. In an interesting report Strauss and Howard claimed that antigens prepared from brains of infected mice give false positive reactions some time after their preparations, as will antigens prepared from brains of normal mice. On the basis of 217 Frei tests made on persons suffering from acute venereal lymphogranuloma and on healthy medical students in which mouse brain antigens of varying age were used, von Haam and Hartwell concluded that neither the specificity nor the sensitivity of such antigens is altered by storage in the ice box (4 C.) or at room temperature (20 C.) for as long as fourteen months.

Sullivan and Ecker criticized the dose of antigen injected, warning that heavy doses may easily produce nonspecific reactions. In reply

Hellerström and Wassén stressed the fact that specific reactions appear delayed; i. e., they appear after forty-eight hours and remain evident for as long as eight to twelve days in contradistinction to nonspecific reactions, which appear earlier and are evanescent.

Coutts recommended as a valuable control for the Frei test a specific complement fixation test for venereal lymphogranuloma; human pus or lymph gland emulsion is used as antigen (Coutts, Landa Perroni and Martini Herrera). On the basis of 300 parallel tests Coutts and Ponce held that any positive Frei reaction appearing about twenty-five days after the onset of the infection is specific. Prats was not able to confirm this conclusion. Gottlieb's report of antigen-neutralizing bodies in the serum of convalescent patients has not been confirmed (Miyagawa and co-workers; Sullivan and Ecker), nor has the observation of Reiss concerning the antigenic properties of human serum obtained in the second or third week of the disease.

THERAPY

There is no better means of expressing the present knowledge of the therapy of venereal lymphogranuloma than to quote the words with which the great continental expert on this disease, Sven Hellerström, introduced his answer to a questionnaire on the subject for a dermatologic journal: "It is a problem which at present is far from being solved even in the hands of the trained specialists." Nevertheless, current medical literature contains an amazing amount of material recommending treatment of the disease by widely different methods. To the critical reader of these reports, however, three facts are evident: 1. Many authors are unaware of the true character of the disease. 2. Comparative investigation of various therapeutic methods by the same author is rare. 3. In most instances the number of patients reported treated is small.

On the basis of clinical and experimental observations we rightly assume that a passing general infection of the organism with the virus is frequent and leads to constitutional symptoms and under certain conditions produces distant lesions in the joints, skin, eyes and other organs (Coutts; von Haam and D'Aunoy). In a certain number of cases, months or years after the acute symptoms of the disease have subsided there occurs elephantiasic enlargement of parts of the external genitalia (labia or scrotum), sometimes with extensive ulceration, followed frequently, especially in the female, by inflammatory stricture of the rectum and severe proctitis. This is still throught by the majority of authors to be a consequence of the destruction of the lymph drainage (Stannus); some, however, regard it as a manifestation of the action of active virus, which still can be demonstrated in the diseased tissues by inoculation of animals (Coutts). While the disease rarely leads to the

death of the afflicted person, it brings much discomfort. Many of its victims are for months or years unable to do any work; they fill the charity clinics and the welfare institutions. Since methods of preventive medicine and public hygiene are still powerless to prevent this infection, it appears logical that every effort should be exerted in attempting to combat the disease successfully when once it is established.

The therapeutic methods advocated can be divided into three general groups: physical, medical and surgical. Gay Prieto emphasized that no treatment is equally successful for all the manifestations or types of venereal lymphogranuloma, and Rousseau and Adamesteanu warned against adopting any one form of therapy. It is advantageous to discuss separately the therapy recommended for the early and that for the late or secondary manifestations of venereal lymphogranuloma.

Treatment of Acute Venereal Lymphogranuloma.—The primary manifestations of venereal lymphogranuloma—small herpetiform lesions, mild urethritis or, in rare instances, phagedenic ulcers—show a marked tendency to heal spontaneously and do not require special therapeutic measures. In most cases the lesion is so minute that it is completely overlooked by the patient, and no evidence of it can be found at the time of examination. The severe constitutional symptoms which are usually present at the onset of the disease can be effectively combated by such general therapeutic measures as rest in bed, adherence to a light diet and purgation. In many cases we observed a favorable action of salicylate, especially acetylsalicylic acid. Quinine, which had been used extensively before the true character of the disease was known (Lesueur-Florent), has no place in the therapy of venereal lymphogranuloma. Most therapeutic efforts have been centered on the specific regional lymphadenitis, which is the principal manifestation of acute venereal lymphogranuloma. The evaluation of methods used in the treatment of lymphogranulomatous adenitis is, as Stannus correctly emphasized, greatly handicapped by the fact that abortive forms occur with much more frequency than has been previously assumed. This may also be the reason why early treatment of the climatic bubo, which includes all the abortive forms, is more successful (Hellerström) than treatment after fluctuation has been observed.

The physical methods employed in the treatment of the acute bubo of venereal lymphogranuloma comprise chiefly galvanic cauterization (von Veress) and irradiation of the bubo with ultraviolet rays, roentgen rays (Nicolas and Favre; Löhe and Blümmers) or radium. None of these methods is credited with outstanding success and should be applied only in combination with medical or surgical treatment.

The medical therapy consists of the use of drugs or biologic products, such as specific and nonspecific vaccines and proteins. Among the

drugs, the antimony preparations have been used most widely in the treatment of acute buboes and have, according to some investigators, proved rather successful. Antimony and potassium tartrate and various commercial preparations (stibenyl [sodium acetylparaaminophenylstibinate], neostibosan [the paraaminophenylstibinate of diethylamine], anthiomaline [the lithium salt of stibiothiomatic acid] and fuadin [sodium antimony biscatecholdisulfonate]) are injected intramuscularly or intravenously, and healing, sometimes without suppuration, is reported to occur in from four to sixteen weeks following their use (Sézary and Lenègre; Sézary, Bolgert and Joseph; Nicolas, Favre, Pétouraud and Chanial). A strong drug reaction is desirable (Sorley and Gibson), and nausea, muscular pains and occasionally severe albuminuria have been produced by rapid injection of such drugs (Mamou). Sézary and Lenègre, on the basis of their experience, doubted the therapeutic value of the antimony preparations. Our own experience with antimony and potassium tartrate confirms the opinion of the French authors to such an extent that we have come to use failure of this type of therapy as a means of differentiating the chronic lesions of venereal lymphogranuloma from similar lesions caused by granuloma inguinale, for which antimony and potassium tartrate is specific. The numerous other remedies recommended by various authors have not been investigated sufficiently to establish their therapeutic value. Iodides (Giacardy), methylthionine chloride (methylene blue) (Araujo), various copper salts (Frei and Wiese), introcid (a cerium-iodine) (Grippain), sodium salicylate (Chevallier and Fiehrer; Touraine and Aubrun), gold salts in the form of solganol (the disodium salt of 4-sulfomethylamino-2-auromercaptobenzene-1-sulfonic acid) (Löhe and Rosenfeld) and glycerin (Pinard and André) have been tried in a small number of cases with varying results. As the most harmless of the drugs mentioned, sodium salicylate has recently found wide use, especially by French dermatologists. It is recommended (Chevallier and Fiehrer) in oral doses of 6 to 8 Gm. a day, accompanied by a strict milk diet in order to avoid gastric complications, or in the form of intravenous injections of sodium salicylic gluconate. Acetylsalicylic acid given in small doses has with us proved an excellent agent in combating the severe constitutional symptoms usually present at the onset of the disease.

With increasing frequency, attempts to treat venereal lymphogranuloma with specific or nonspecific vaccines or proteins are reported. The fact that these agents are usually less harmful than the heavy metals recommends at least their trial, although the number of reported "cures" is at present not sufficient to warrant any conclusions. Injections of milk (Tissot), T. A. B. (typhoid, paratyphoid A and paratyphoid B) vaccine (Hanschell, Lorn and Cooke), tuberculin and pyrifer (a nonspecific protein mixture prepared with extracts of fever-producing

bacteria from nonpathologic stocks) (Löhe) apparently have a tendency to hasten the maturation of the glands, while specific vaccines prepared from pus or emulsions of glands from persons afflicted with the disease or from organs of animals experimentally inoculated with the virus are supposed to bring about resolution of the process without suppuration. Hellerström, who initiated specific vaccine therapy for venereal lymphogranuloma, recommended slow desensitization of the allergic patient by small repeated intravenous injections of Frei's antigen (Chevallier and Fiehrer; Ravaut, Levaditi and Maisler), and Gay Prieto, as a result of his experience in 3 cases, looked on this treatment as the method of choice. Ionesco-Mihaiesti, Longhin and Wisner observed healing of the lesions in 6 cases after one to five intravenous injections of from 0.2 to 0.5 cc. of antigen. Wien and Perlstein reported marked improvement of patients even after a single diagnostic intradermal injection. Kalz and Sagher reported that in 30 patients treated by intramuscular injections of convalescent serum healing of the lesions occurred in about six weeks, and Tamura recommended treatment of acute buboes with specific antilymphogranuloma goat serum—a method which resulted in cure in 3 cases after an average duration of the disease of eight weeks.

Surgical treatment of the infection in the acute stage must still be regarded as the most popular method of therapy, although it has recently been criticized severely by those who regard venereal lymphogranuloma as a systemic infection. Simple aspiration of the fluctuating glandular masses with or without subsequent injection of an antiseptic solution, broad incisions with drainage, and more or less extensive extirpation of the enlarged glands were used long before the causal agent of the disease was known. That surgical therapy still holds its place in the treatment of acute venereal lymphogranuloma can be seen from the fact that in many of the recent publications advocating different methods of treatment reference is still made to surgical treatment as a last resource in dealing with obstinate lesions. Opponents of surgical intervention (Löhe; Sézary and Lenègre) emphasized such undesirable end results as slow-healing wounds and, as a consequence of the destruction of the lymph drainage, postoperative elephantiasis of the genitalia. Those in favor of surgical treatment (Rousseau and Adamesteanu; Ruge) stressed the great acceleration of complete healing (three to six weeks) with immediate relief of local pain as great advantages. While we with others (Coutts; Stannus) have shown that general infection occurs in the course of venereal lymphogranuloma in a rather large number of cases, we have noted also that only local lesions can be observed in the majority of patients, owing to the rapid destruction of the virus in the human organism. Removal of the local lesions, therefore,

would remove the main source of possible further spread of the infection and is a biologically correct method of treatment. This fact will gain in importance if it is ever proved that the virus of venereal lymphogranuloma, like other true pathogenic viruses, multiplies only intracellularly. Another possible advantage of surgical therapy was pointed out by Jersild, who observed that partial adenectomy or only simple incision of a superficial bubo results in marked improvement in the deeper seated lymph glands. He explained this observation, which was confirmed by Hellerström, Rousseau and others, on the basis of autovaccination with antigen through the operative wound. The necessity of surgical intervention in cases of secondary infection with massive suppuration is generally admitted.

In our investigation of appropriate methods of treatment, 85 patients in whom the disease had been diagnosed clinically and immunologically were submitted to operative procedures and carefully observed as regards healing of the lesions and general improvement. In order to avoid the abortive form, which will heal under any therapy, we did not follow Hellerström's advice of early operation but treated all patients conservatively until the size and the consistency of the glands made spontaneous regression of the lesions appear improbable.

Partial adenectomy resulted in healing of the lesions one month after operation in over 50 per cent of the cases. Simple incision with drainage delayed the healing process in the majority of cases for from two to four weeks. Nineteen cases of abortive venereal lymphogranuloma came under observation during the period of study. In these the infection was extremely mild, without suppuration. Disappearance of the glands, or spontaneous cure, was observed in the majority of these cases after four to six weeks—a period as long as was required for healing of the acute suppurating bubo after surgical therapy. The average period of the disease was four and seven-tenths weeks for the cases in which treatment was by partial adenectomy, five weeks for those in which treatment was by incision and drainage and six and two-tenths weeks for those in which the disease was abortive, with spontaneous cure. Eight months after conclusion of the investigation none of the 85 surgically treated patients had chronic edema or elephantiasis of the genitalia, although in 27 per cent bilateral lesions were still present. These results led us to conclude that surgical intervention in acute venereal lymphogranuloma can be regarded as a successful method of therapy, partial adenectomy resulting in earlier healing of the suppurating bubo than simple incision and drainage.

Treatment of Chronic Venereal Lymphogranuloma.—While therapeutic management of the acute lesions of venereal lymphogranuloma can claim at least some degree of success, treatment of the late or chronic

lesions gives most unsatisfactory results. Modern concepts of the evolution of this infectious venereal disease, however, may explain the failure in the therapy of its chronic manifestations—esthiomène, or ulcerative elephantiasis, and inflammatory stricture of the rectum. Except in the rare cases in which general dissemination of the virus can be established, the infectious agent inhabits chiefly the lymph glands in the region of the primary infection and has a tendency, after destruction of the glandular tissue, to spread locally. Through lymph stasis in the tissues in which the lymph drainage has been interrupted by destruction of the glands, chronic edema is produced. The inflammatory process spreading retrograde along the lymph vessels and in adjacent tissues results in the production of a characteristic granulation tissue with numerous small abscesses and sinuses, the lesion showing a marked tendency toward massive hyperplastic fibrosis. The development of chronic manifestations depends largely on the location of the affected lymph glands, which correctly must be regarded as the center of the pathologic process. If the inguinal, presymphysial or crural lymph nodes are involved, the external genitalia (scrotum, penis and vulva) bear the brunt of the spreading infection, and elephantiasis of the affected part will develop. Infection of the anorectal, deep iliac and sacral glands causes disease of the perineum and rectum—the genitoanorectal syndrome, or venereal lymphogranuloma of the perineum and inflammatory stricture of the rectum. The skin and mucous membranes covering the edematous tissues suffer considerably from nutritive disturbances caused by the chronic lymphedema, and this allows penetration of secondary invaders into the subepithelial structures. Thus severe infections are established in already altered tissues, hastening their complete destruction. This secondary infection of tissues infected with the virus of venereal lymphogranuloma is an important complication, producing severe ulceration in the instances of elephantiasis—described as esthiomène—and severe proctitis in the cases of rectal stricture.

From this brief sketch of the development of the chronic lesions of venereal lymphogranuloma it is possible to realize how futile therapy will be when the process is advanced, the lesions then often representing merely an end result of the disease complicated by various secondary pyogenic infections. The only relief the patient can expect is a temporary cure of the ulcers in the rectum and on the genitalia. The truth of this statement is well borne out by practical experience in the treatment of esthiomène and rectal stricture. Surgical excision of the parts suffering from elephantiasis is the ideal way of treating esthiomène, but it is only possible when the areas of the genitalia involved are small. Antisyphilitic therapy and the injection of antimony and potassium tartrate have met more with failure than with success and cannot be

recommended. The specific treatment with vaccines or Frei antigen has not been studied sufficiently to permit any conclusion, but in the few cases in which it has been used it has not given very encouraging results. There is no effective method of treatment for rectal stricture. According to C. F. Martin, the disease in this stage may be described as incurable, tending inevitably toward a fatal termination. Resection of the rectum, sigmoid, perirectal tissues and perineum has brought permanent relief but is a drastic procedure (Lee and Vander Veer). Simple extirpation of the rectum does not remove the principal site of the pathologic process, and therefore recurrence will be observed in a large number of the cases in which this treatment is tried (Gatellier and Weiss). Colostomy is often a necessary emergency procedure and in most cases must remain permanent. It carries a mortality of about 30 per cent. Gohrbrandt suggested sloganol (the disodium salt of 4-sulfomethylamino-2-auromercaptobenzene-1-sulfonic acid) for the treatment of rectal stricture in the early stage, and G. M. Brown observed favorable results from the use of diathermy. Gay Prieto observed a case in which distinct improvement followed intravenous injection of Frei antigen. A similar observation was made by Alley, who treated 9 patients for mild stricture of the rectum with intradermal injections of antigen and obtained "encouraging results." In the Charity Hospital of Louisiana at New Orleans repeated dilatation of the stricture is the adopted procedure in all cases in which the condition is not too far advanced, and it has met with fair success in that it delays the more serious symptoms, which as a rule require colostomy.

Attention should be directed most intensively toward prevention of this incurable form of venereal lymphogranuloma through proper therapeutic management of the infection in the acute stage. In the female this stage is frequently not discernible, owing to the deep location of the affected glands, which also prevents possibly effective early treatment, and this explains the greater prevalence of chronic, inoperable, incurable venereal lymphogranuloma in such patients.

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Notes and News

University News, Promotions, Resignations, Appointments, Deaths, Etc.—Columbia University has conferred the title of professor emeritus on Francis Carter Wood, director of the Crocker Institute of Cancer Research.

Lieut. Col. A. Parker Hitchens, Medical Corps, U. S. A., has been appointed George S. Pepper professor of public health and preventive medicine in the University of Pennsylvania.

Alexander S. Wiener, Brooklyn, has been appointed bacteriologist and serologist in the office of the chief medical examiner of New York.

Alexis Carrel, Karl Landsteiner, Phoebus A. T. Levene, W. J. V. Osterhout and Florence R. Sabin are retiring from active work in the Rockefeller Institute for Medical Research, according to the retirement rule.

Frederick P. Gay, professor of bacteriology, Columbia University, New York, and William B. Castle, associate professor of medicine, Harvard Medical School, Boston, have been elected members of the National Academy of Sciences.

Francis Amory Prize.—In compliance with the will of the late Francis Amory, of Beverly, Mass., the American Academy of Arts and Sciences announces a septennial prize for outstanding work on the alleviation or cure of diseases affecting the human genital organs, to be known as the Francis Amory Septennial Prize. The prize may be awarded to any person or group for work of "extraordinary or exceptional merit" in this field. In case there is work of a quality to warrant it, the first award, which will exceed $10,000, will be made in 1940. It may be given in one or more awards. Further information will be furnished by the Amory Fund Committee, care of the American Academy of Arts and Sciences, 28 Newbury Street, Boston.

Dazian Foundation.—The Dazian Foundation for Medical Research is prepared to award fellowships to persons holding the degree of Doctor of Medicine for the purpose of postgraduate study and research, and grants to laboratories, hospitals and similar institutions for research in medicine. Applications and inquiries should be directed to the Secretary, 180 East Sixty-Fourth Street, New York.

Society News.—The Chicago Pathological Society has elected the following officers: S. A. Levinson, president; George Rukstinat, vice president; Edwin F. Hirsch, secretary, and A. A. Goldsmith, treasurer.

Awards.—The George M. Kober medal was presented to George H. Whipple at the meeting of the Association of American Physicians in Atlantic City, May 3.

James B. Herrick has been awarded the distinguished service medal of the American Medical Association.

The Burdick Award for an "outstanding contribution to medical science" was given by the American Society of Clinical Pathologists at its recent meeting in St. Louis to Harry Goldblatt for his work on hypertension and the relation between high blood pressure and renal disease.

Abstracts from Current Literature

To Save Space the Original Titles of Abstracted Articles Sometimes Are Shortened

Experimental Pathology and Pathologic Physiology

Experimental Streptococcic Endocarditis. R. A. Kinsella and R. O. Muether, Arch. Int. Med. **62**:247, 1938.

Seventeen dogs were subjected to operations whereby the mitral valve or the chordae tendineae were cut. All these animals were then fed with living cultures of nonhemolytic streptococci, which were either mixed with their food or given by stomach tube. Ten of the animals became sick; cultures of their blood showed growth of hemolytic streptococci, and the animals died. At autopsy these infected dogs had bacterial endocarditis. The bacteria in the vegetations were determined to be identical with those which had been fed to the animals. Streptococcic endocarditis can be produced in dogs with injured cardiac valves by feeding them streptococci. The fact is thus established that bacteria entering the animal body through the mouth may become implanted on an injured area within the body. The exact route which these bacteria follow has not been determined.

The reproduction of streptococcic endocarditis is complete. The success of two different drugs in curing the disease in dogs while failing to cure the disease in human beings does not obscure the identity of the experimental disease. On the other hand, the difference between the mode of production of the experimental disease and the mode of production of the disease in human beings is emphasized. This difference lies in the fact that bacterial implantation begins after an injury produced by trauma in the one instance and as a result of disease in the other. It seems highly important to collect a series of animals cured of streptococcic endocarditis and then to study the treatment after reinfection of the healed scars of previous infection. This will be a tedious task. The most interesting by-product of the present study has been the demonstration of infection of traumatized valves through feeding streptococci to animals. This part of the work, repeated in different years, seems adequately authenticated. It is of further interest that none of the microscopic appearances in the heart or elsewhere was such as to suggest a relation between the lesions observed in dogs and those of rheumatic fever which appear in human tissues.

From Authors' Summary.

Experimental Staphylococcus Osteomyelitis. R. H. S. Thompson and R. J. Dubos, J. Exper. Med. **68**:191, 1938.

The results indicate that it is possible to produce consistently inflammation of the bones of rabbits merely by injecting intravenously a suitable strain of Staphylococcus, without resorting to any elaborate operative technic designed to localize the organisms in the bones. It appears also that the inflammatory process so produced bears a close resemblance to staphylococcic osteomyelitis occurring in human beings.

From Authors' Summary.

Neuron Degeneration in Vitamin Deficiency. M. M. Wintrobe, D. M. Mitchell and L. C. Kolb, J. Exper. Med. **68**:207, 1938.

Young pigs were given an artificial diet which was presumably adequate in all respects. As they developed, the quantity of yeast was gradually reduced while thiamin (vitamin B) and riboflavin were given in its place. The rate of

growth of the animals decreased, their general condition became impaired, and marked ataxia without motor weakness developed. Histologically the posterior columns of the spinal cord, the dorsal root ganglion cells and the peripheral nerves showed severe degeneration. FROM AUTHORS' SUMMARY.

FUNCTIONAL HYPERPLASIA OF THE PARATHYROIDS. A. B. EISLER, Brit. J. Exper. Path. **19**:342, 1938.

Data are presented which show that significant hyperplasia of the parathyroid glands occurs without concomitant renal damages in rabbits with toxic anemia. The cause of this hyperplasia is discussed with respect to the relation between calcium metabolism and detoxication. FROM AUTHOR'S SUMMARY.

ORGAN HYPERTROPHY IN THYROID-FED RATS. O. L. V. S. DE WESSELOW and W. J. GRIFFITHS, Brit. J. Exper. Path. **19**:347, 1938.

The adrenal medulla is not concerned with hypertrophy of the heart and other organs of rats fed desiccated thyroid substance. The drug 2,4-dinitrophenol, which increases the rate of metabolism of the tissue in general, does not produce hypertrophy of the organs of the rat. Since increasing the rate of the consumption of oxygen by the tissues does not of itself result in cardiac hypertrophy, the effect of thyroid on the heart cannot be ascribed to this aspect of its function. The increase in metabolism and the tachycardia, although they develop simultaneously under the action of thyroid, are unrelated. It is probable that the hypertrophy of the heart is secondary to the increase in the rate of contraction and the extra work performed. FROM AUTHORS' SUMMARY.

Pathologic Anatomy

INFARCTION OF THE HEART. W. B. BEAN, Am. Heart J. **14**:684, 1937.

This is a study of 300 necropsies which disclosed infarction of the heart, selected from 9,626 consecutive necropsies in the Boston City Hospital in the years from 1906 to 1936. Among the patients there was a predominance of males—69.7 per cent. The average ages were 60.1 for males and 61.7 for females. The seventh decade of life showed the largest incidence of infarcts. The first attack was recorded at an earlier age in the case of males than in that of females. A family tendency toward cardiovascular disease and hypertension appeared as a contributory factor; obesity seemed also to be contributory, though thinness did not protect against infarction. Diabetes and disease of the gallbladder were factors, but merely by virtue of the arteriosclerosis with which they were invariably associated. Alcohol and tobacco did not seem etiologically important. The incidence of infarction was significantly low during the summer. In the presence of disease of the coronary arteries a surgical or medical shock acted as a precipitant of coronary thrombosis. I. DAVIDSOHN.

INCIDENCE OF MYOCARDIAL INFARCTION WITHOUT PAIN IN TWO HUNDRED AUTOPSIED CASES. J. A. KENNEDY, Am. Heart J. **14**:703, 1937.

In 4 per cent of the cases of myocardial infarct occurring within eight weeks before death, carefully taken histories failed to reveal any sensation of pain in relation to the infarct. Among old infarcts from which the patients recovered, the number of painless ones was larger (about 22 per cent). Kennedy emphasizes that in about one third of the cases of infarct recorded the circumstances were such that it was impossible to elicit a history of pain and that therefore such infarcts must be excluded. I. DAVIDSOHN.

ENDOMETRIUM IN PREGNANCY. A. C. BRODERS and J. R. MCDONALD, Am. J. Clin. Path. **8**:547, 1938.

During the early part of pregnancy the endometrium usually presents a picture more or less comparable to that of the late differentiative phase of the menstrual cycle. This picture is less common in extrauterine pregnancy. The changes in the endometrial glands ("glands of pregnancy") are present in a large proportion of cases of early uterine pregnancy and in a small proportion of cases of extrauterine pregnancy. Occasionally they are seen in the agravid uterus immediately prior to the menstrual period. "The glands of pregnancy" have the same significance as decidual tissue. Decidual tissue was found in the uterus in 5 of 27 cases of extrauterine pregnancy.

FROM AUTHORS' SUMMARY.

STRUCTURE OF THE FILUM TERMINALE. I. M. TARLOV, Arch. Neurol. & Psychiat. **40**:1, 1938.

The filum terminale is a slender band connecting the last two segments of the spinal cord, i. e. the conus medullaris, with the coccyx. The dura follows the filum down to the second sacral vertebra. The intradural portion of the filum has a definite nerve structure, containing gray matter (small and large multipolar cells), a central canal and nerve-fibers. The gray matter cannot be differentiated from the white substance, both containing numerous ependymal cells and also oligodendrocytes and astrocytes. In the extradural portion of the filum the microglia and neuroglia are replaced by Schwann and endoneurial cells. The nerve fibers of the filum run within its connective tissue sheath and are invested with endoneurial and Schwann cells and form bundles. In an adult film products of degeneration occur in the form of corpora amylacea, which are reticulin balls derived from the connective tissue of the filum, staining reddish with Rio Hortega's lithium–silver carbonate.

G. B. HASSIN.

THE THECA INTERNA CONE AND ITS ROLE IN OVULATION. E. O. STRASSMAN, Surg., Gynec. & Obst. **67**: 299, 1938.

Ovulation is a mechanical process stimulated by the endocrine glands. Its mechanism can be understood only by determining how the graafian follicle reaches the surface of the ovary. A study based on more than 18,000 serial sections of ovaries from human and other mammals, including Carnivora (rat and dog), Rodentia (rabbit) and Ungulata (swine, cow, horse), has demonstrated eccentric growth of the theca interna of the growing follicle. This one-sided proliferation of the theca interna is always directed toward the surface of the ovary, forming a cone, wedge shaped on the cut surface and infiltrating and penetrating the surrounding tissues, thus making a path for the growing follicle. The maturing follicle ascends to the surface of the ovary by following the line of least resistance which is provided by the cone of the theca interna. The average distance between follicle and ovarian surface becomes shorter with the appearance of the thecal proliferation. In human and mammalian ovaries, which have much free ovarian surface, the axis of the thecal cone is directed toward the nearest point on the surface of the ovary. In horses, in which the surface of the ovary is surrounded by connective tissue (mesovarium), the axis of the cone of the theca interna is directed toward the only free spot on the surface of the gland, namely, the ovulatory fossa. The wedge-shaped cone can be demonstrated only in the sections which run through the apex of the cone perpendicularly toward the ovarian surface. A more or less marked degree of edema is present in the surrounding tissues, which facilitates the mechanical progress of the ascending follicle.

FROM AUTHOR'S SUMMARY (WARREN C. HUNTER).

A Histological Study of the Mummy of Har-mosĕ. A. F. B. Shaw, J. Path. & Bact. **47**:115, 1938.

An account is given of the mummy of Har-mosĕ, the lute player and singer of the eighteenth dynasty, who died about 1490 B. C. The organs (lung, liver, gall-bladder, mesentery and intestines) found in the canopic chest were in a remarkably good state of preservation and superior in this respect to any mummified tissues hitherto described from Egypt. The reasons for this were not determined. It was found that the supporting tissues of the organs, especially collagen, cartilage matrix, elastic fibers and argyrophil reticulum, were preserved almost in their original state. For this reason stains which differentiate these elements gave the best results. Although the cytoplasm of unstriped muscle, liver cells and fat cells and of the epithelium of the bronchi, intestines and gallbladder had survived, the nuclei had disappeared. There were no cells in the parenchyma of the lung or in the pleura. The blood vessels sometimes contained material giving the staining reactions of hemoglobin, but erythrocytes and leukocytes were never seen. From the distribution and amount of adipose tissue in the mesentery and around the gallbladder it seems probable that Har-mosĕ was a fat man or at least well nourished. Pathologically the deceased Egyptian showed pulmonary anthracosis and emphysema, an old pleural adhesion, intimal thickening of the superior mesenteric artery and fatty involution of the pulmonary lymph nodes. The two latter lesions may have been due to his age. Evidence is produced in support of the view that Har-mosĕ probably suffered from acute bronchopneumonia and pleurisy, which from their extent must have been the immediate cause of his death.

From Author's Summary.

Acidophilic Cell "Inclusions" in Nerve Tissue and in Kidneys of "Normal" Pigeons. S. Nicolau and L. Kopciowska, Ann. Inst. Pasteur **60**:308, 1938.

Three varieties of strongly eosinophilic bodies similar to inclusion bodies have been found in the nerve cells of "normal" pigeons." These bodies varied from minute granules to round or oval structures from 3 to 4 microns in diameter and occurred both singly and in groups. Irregular masses of granules were found in the cytoplasm of brain cells. In the nuclei of spinal ganglion cells bodies were seen which often showed an internal structure similar to that of Borna's inclusions. Cytoplasmic inclusions with a complex internal structure were found in the spinal ganglions.

Both cytoplasmic and nuclear inclusions were present in the cortex of the kidney, the nuclear ones being the more frequent. The bodies were rounded refractile structures from 1 to 5 microns in diameter.

Some birds showed only one variety of inclusion, but in others all of these forms were seen. In some of the pigeons interstitial infiltration and perivasculitis of nerve tissue were observed, but inclusions were also present in birds without other histologic changes.

There may be many unknown viruses which do not produce clinical symptoms but only histologic changes and inapparent, i. e. latent, infection.

J. B. Gunnison.

Myocardial Changes in Diphtheria. L. Oheim, Beitr. z. path. Anat. u. z. allg. Path. **100**:195, 1938.

A morphologic study of the myocardium in 50 fatal cases of diphtheria in which there were no complicating infections or other complicating conditions revealed the following successive changes: interstitial edema, myolysis, waxy degeneration, calcification, fatty degeneration, proliferation of fixed cells in the spaces arising from muscle cell degeneration, and leukocytic and lymphocytic infiltrations. Interstitial edema and initial myolysis appeared first on the second to the fourth day of the disease, while the other changes reached their height of intensity from the seventh to the thirteenth day. Reparation by connective tissue proliferation had

commenced by the tenth day. The most severe lesions were encountered in the subendocardial and ring muscle layers of the myocardium, especially of that of the right ventricle. The significance of this distribution in respect to the efficacy of intravenous therapy is discussed.

R. J. LEBOWICH.

SCLEROSIS OF ARTERIOLES OF THE SPLEEN AND KIDNEY IN RELATION TO ARTERIAL HYPERTENSION. K. SCRIBA, Virchows Arch. f. path. Anat. **301**:321, 1938.

This is a contribution from Fahr's institute on the still unsolved problem of the interrelationship of arteriolosclerosis and arterial hypertension. It is based on histologic examination of the arterioles of the spleen and kidney in a series of 132 subjects aged from 3 months to 82 years; 56 had not had hypertension during life and 76 had. The presence of hypertension was determined by the readings of blood pressure made during life or by the observation of left ventricular hypertrophy at necropsy. The spleen was included in the investigation because of its functional activity and its reaction to infection, toxemia and other general conditions, factors which Scriba believed might be important in the development of arteriolosclerosis. In the first five decades of life arteriolosclerosis was as frequent or even more frequent in the spleen and kidney in nonhypertensive persons as in those with hypertension. From the fifth decade on sclerosis of arterioles became progressively more frequent in those who had had hypertension. Scriba interprets his observations as indicating that the etiologic factors in the development of arteriolosclerosis are local functional reactions of the organ to mechanical or toxic factors, the constitutional element, various dyscrasias and age. Arterial hypertension is not the cause of arteriolosclerosis but is at most only an accessory factor.

O. T. SCHULTZ.

ORIGIN OF THE INTRAEPITHELIAL HYALINE DROPLETS OF THE KIDNEY. A. HEIN, Virchows Arch. f. path. Anat. **301**:339, 1938.

To determine the origin and significance of the hyaline droplets of the epithelium of the main convoluted tubules of the kidney which are observed in association with albuminuria, Hein injected solutions of proteins into the abdominal cavity of the salamander. Human blood serum and its fractions and solution of egg white were used in varying amounts and over varying periods. Hyaline droplets of albuminous material appeared in the convoluted tubular epithelium. A prerequisite for their presence was the presence of protein in the lumen of the tubules, arrived there through the open nephrons in the case of proteins with large molecules and through the glomeruli in the case of molecules of smaller size. The droplets were formed in the reabsorption by the tubular epithelium of the protein from the lumen. The process was one of temporary storage of absorbed material. A certain amount of protein injected over a short period caused a more marked formation of droplets than the same quantity administered over a longer period of days. Albumose derived from commercial peptone also caused the formation of hyaline droplets. Cessation of the administration of proteins was followed by disappearance of the droplets. The tubular epithelium may utilize or break down the stored absorbed protein.

O. T. SCHULTZ.

THE VASCULAR CHANGES IN VARIOUS TYPES OF PULMONARY TUBERCULOSIS. B. NEUBERT, Virchows Arch. f. path. Anat. **301**:364, 1938.

The types of pulmonary tuberculosis selected for investigation were the primary focus, caseous pneumonia, bronchogenic aspiration tuberculosis, lymphogenous productive tuberculosis, hematogenous spread, giving rise to miliary tuberculosis, and cavernous tuberculosis. The vascular reaction may be specific or nonspecific. In the latter, a diffuse proliferative process leads to partial or complete obliteration of the blood vessel. In each type of tuberculosis the character of the vas-

cular reaction was noted, whether specific or nonspecific, and the number of vessels in the tuberculous area and in the adjacent parenchyma revealing partial (one fourth) to complete obliteration was tabulated. Obliterated vessels were most numerous in the primary focus and least numerous in the hematogenous form of spread. In general, obliterated vessels were more numerous in fairly rapidly progressing lesions than in more slowly progressing ones, except that caseous pneumonia may progress so rapidly that there is not time for an obliterating reaction on the part of the vessels. Nonspecific obliteration in the peripheral zone of nontuberculous inflammation precedes the advancing spread of the parenchymatous process. The character of the parenchymatous involvement is not dependent on the vascular change, but the latter may hasten the progress of tissue destruction.

O. T. SCHULTZ.

CORRELATION OF FETAL BODY LENGTH WITH THE WEIGHTS OF ORGANS. A. GIORDANO, Virchows Arch. f. path. Anat. **301**:380, 1938.

This is a correlation of body length with the weights of the heart, lungs, liver, spleen and kidneys, according to accepted current methods of statistical analysis. This conclusion is based on a study of 445 infants, dead at birth or shortly after birth, and varying in length from 30 to 67 cm. The females in the series numbered 199 and the males 246. A striking feature of this series is that 25 per cent of the infants had a body length of from 52 to 67 cm., indicating a duration of pregnancy beyond the normal limit. The high mortality in this group was due to intracranial hemorrhage. It suggests the advisability of terminating pregnancy at the normal term. The weights of the organs in the various length groups are expressed in tables and graphs. In the length groups 40 to 47 cm. and 47 to 52 cm. the organ weights were practically the same for both males and females. In both males and females the rate of increase in organ weights was greater at body lengths of from 47 to 52 cm. than in younger fetuses with lesser body lengths. In the length group 52 to 67 cm., representing a prolonged duration of pregnancy, organ weights increased somewhat less rapidly, but the organ weights of males were decidedly greater than those of females in this group.

O. T. SCHULTZ.

Pathologic Chemistry and Physics

BLOOD PLASMA PROTEINS AND LIVER INJURY. C. C. ERICKSON, G. P. HECKEL and R. E. KNUTTI, Am. J. Path. **14**:537, 1938.

By frequent oral administration of carbon tetrachloride to dogs it has been possible to produce moderate cirrhotic changes in their livers. In such animals the plasma protein concentration falls slightly, and this fall appears to be due largely to loss of albumin. Continued oral administration of acacia combined with carbon tetrachloride results in deposition of what appears to be acacia in hepatic cells, as in the case of administration of acacia alone. Other sites of deposition of acacia in dogs receiving carbon tetrachloride and acacia appear to be the sinusoidal lining cells of the spleen and the large mononuclear phagocytic cells which have been found in sparse numbers in the lungs, spleen, lymph nodes and bone marrow. Clinically these animals remain in remarkably good condition, and, although the concentration of their plasma protein may be well below the edema level, there has been no evidence of edema. The bleeding time of such dogs is prolonged, and this is thought to be associated with low concentration of fibrinogen, although the possibility of a scanty supply of prothrombin must also be considered. The diminution of the concentration of plasma protein is somewhat more marked in animals receiving carbon tetrachloride and acacia than in those receiving either of these substances alone. This is particularly true of changes in the concentration of fibrinogen. The reactions of albumin, globulin and fibrinogen to various

types of hepatic injury indicate that these substances may be produced independently of each other and that the liver is concerned in their production.

From Authors' Summary.

p_H in Pneumococcus Exudates. W. H. Kelley, E. N. Scadron and B. M. Shinners, J. Exper. Med. **67**:659, 1938.

The hydrogen ion concentration in the lesions of experimental pneumococcic infection has been estimated directly by determinations of p_H on exudates from living animals. For indirect evidence of an increase in hydrogen ion concentration within the lesions, the difference in sugar content between exudate and blood from animals with pneumococcic infection has been measured. With sanguineous exudate from the consolidated lungs of dogs with experimental pneumococcic pneumonia, the findings were not always consistent, but usually there was either direct or indirect evidence of increased hydrogen ion concentration. The physicochemical changes in exudate from animals treated with artificial pneumothorax showed no important differences from those in other specimens. In concurrence with Lord's observation of increased acidity of pneumonic exudate obtained at autopsy, sugar concentrations, which are low in the blood, were markedly reduced in exudates from animals which had died of the infection. Serous exudates from dermal pneumococcic infection in rabbits uniformly showed definite acidity by both direct and indirect methods of estimation. The hydrogen ion concentration in exudate from dermal pneumococcic infection in rabbits varied between p_H 6.87 and 6.66 but was not always proportional to the difference in sugar concentration between the exudate and the blood. While the hydrogen ion concentration of pneumonic exudate from rabbits is similar to that attained in the pneumonic exudate from dogs, it is of lesser magnitude than that which Takahashi has described in the pus of empyema secondary to infection with Pneumococcus.

From Authors' Summary.

Demonstration of Plasma Anticoagulant in Exudates of Bacterial Origin. E. Neter, J. Infect. Dis. **63**:193, 1938.

Exudates of bacterial origin may inhibit the coagulation of human plasma. The purulent exudates tested comprised human spinal, empyemic and peritoneal fluids as well as the contents of abscesses. The micro-organisms recovered from such anticoagulating exudates were Streptococcus haemolyticus, Streptococcus faecalis, Staphylococcus, Pneumococcus, Haemophilus influenzae, Bacillus coli and Clostridium welchii.

Human pneumococcic exudates contained anticoagulant less frequently than those in which the enterococcus was present. Exudates due to the hemolytic streptococcus may contain either anticoagulant or fibrinolysin or both—or such exudates may lack fibrinolytic as well as anticogulating properties.

From Author's Summary.

Law of Chemical Equilibrium in Biology. F. C. McLean, Physiol. Rev. **18**:495, 1938.

So far as McLean is aware, this is the first attempt to review the contributions of the law of chemical equilibrium to the study of biologic problems. It might be thought a priori that this law, being a statement of the conditions in a chemical system at equilibrium, might be of very limited application to biologic processes. On the contrary, its role in the elucidation of the mechanisms of the acid-base balance and in the discovery of physiologically important properties of hemoglobin can hardly be overestimated, and it has opened the way for equally significant progress in the understanding of the complexities of intermediary metabolism. It should be increasingly useful as biology becomes more and more concerned with the analysis of chemical processes in the living organism.

From Author's Conclusion.

A Special Form of Erythrocyte Possessing Increased Resistance to Hypotonic Saline. A. M. Barrett, J. Path. & Bact. **46**:603, 1938.

A special morphologic type of red corpuscle is described which is constantly associated with the presence in the blood of an increased proportion of corpuscles resistant to 0.3 per cent sodium chloride solution. Evidence is given that corpuscles of this type themselves possess increased resistance to hypotonic saline solution. In stained dry films such corpuscles have a characteristic appearance to which Barrett has applied the term "target corpuscle"; in wet films, however, these corpuscles are bowl shaped. In a solution of formaldehyde the corpuscles assumed the target appearance, and it was thus possible to observe the actual shape of the target corpuscle. The correctness of the conclusions regarding the actual shape of the cells in dry and in wet films is shown by roentgen photographs of plasticine models. Evidence is given that in blood containing cells of this type the red corpuscles are abnormally thin. The relationship between the shape of erythrocytes and their resistance to hypotonic salt solution is discussed.

From Author's Summary.

Histochemistry of the Adrenal Medulla. F. Schultz, Beitr. z. path. Anat. u. z. allg. Path. **101**:32, 1938.

In frozen sections of formaldehyde-fixed adrenal medulla from horses, cattle, goats, sheep and hogs it is possible to demonstrate, by means of a stain composed of thionine and tartaric acid, a metachromatic yellow-staining substance of lipoid character. The reaction may be an oxidation of some lipoid-like substance. The yellow coloration is brought out by 95 per cent alcohol and is most intense in adrenal medulla from horses and cattle and less marked in that from hogs, sheep and goats. A similar substance was shown to be present in human adrenal medulla by Feyrtet in 1936.

R. J. Lebowich.

Microbiology and Parasitology

The Incidence of Extrapulmonary Primary Tuberculosis. H. C. Sweany and W. L. M. Martinsen, Am. Rev. Tuberc. **37**:465, 1938.

The records of 132 autopsies were reviewed with attention being paid to calcified foci to determine the percentage of infections from each portal of entry. The lungs and hilar lymph nodes were involved in 73.5 per cent of isolated primary infections, or in 79 per cent of infections if one adds those in which there were multiple portals of entry. The gastrointestinal tract was the portal for 8.3 per cent of isolated infections and for 12.9 per cent of infections if one adds those in which there were multiple portals of entry. The cervical or head region was the portal for 1.8 per cent of isolated primary infections and for 4.5 per cent of infections if one adds those with multiple portals of entry. Three (2.3 per cent) of the primary infections were pleural infections. In three (3.3 per cent) of the cases "cryptic" lesions occurred in the liver or lymph nodes with no demonstrable local lesions. There were 3 (2.3 per cent) cases in which the portal was doubtful and 7 (5.3 per cent) in which no calcifications were found. (In 71 cases no roentgenograms of the neck were made.) In 30.6 per cent of the cases primary hematogenous calcifications were observed in the liver and spleen.

H. J. Corper.

Coccidioidomycosis: The Preliminary Acute Infection with Fungus Coccidioides. Ernest C. Dickson, J. A. M. A. **111**:1362, 1938.

The preliminary illness caused by infection with the fungus coccidioides has been recognized. The disease is caused by inhalation of the chlamydospores, which are formed in the vegetative phase of growth of the fungus. It is a form of infection of the respiratory tract, in many cases accompanied by erythema nodosum, and the great majority of patients recover promptly without complications. The

incidence of erythema nodosum is very high but not constant. When this condition occurs the disease is known in the San Joaquin Valley as "valley fever" or "desert fever." The acute illness, whether or not there is erythema nodosum, may progress to coccidioidal granuloma.

FROM AUTHOR'S SUMMARY.

VIRUS OF MENINGITIS AND PNEUMONITIS. T. FRANCIS JR. and T. P. MAGILL, J. Exper. Med. **68**:147, 1938.

An infectious agent is described which belongs apparently to the class of filtrable viruses but which on the basis of the evidence at hand is not to be identified with any virus previously described. It has multiple tropisms and is pathogenic for mice, for ferrets and for monkeys of the species Macacus rhesus and Macacus cynomolgos. Mice and ferrets infected intranasally show extensive pneumonic lesions of fatal severity. Monkeys inoculated intracerebrally show lymphocytic choriomeningitis, from which they recover, while mice similarly inoculated show rapidly fatal choriomeningitis. Mice which receive the virus by intraperitoneal or subcutaneous routes show fatal paralysis in a moderate proportion of their number, while the remainder become immune according to the intracerebral test but not according to the intranasal test. In mice, monkeys, ferrets, rabbits and guinea pigs subcutaneous inoculation causes local granulomatous induration of the skin with enlargement of the regional lymph nodes. In 1936 ferrets inoculated with throat washings of patients suffering from an epidemic disease clinically indistinguishable from epidemic influenza yielded the virus repeatedly. It is impossible, however, to draw any conclusion as to whether the virus has its origin in ferrets or in man. Although the new agent possesses many features in common with the virus of lymphocytic choriomeningitis and the virus of lymphogranuloma venereum, cross immunity tests have failed to yield any evidence that it is immunologically related to either of these viruses. For purposes of identification, the name "virus of acute meningopneumonitis" is suggested.

FROM AUTHORS' SUMMARY.

VIRUS OF EQUINE ENCEPHALOMYELITIS. P. K. OLITSKY and C. G. HARFORD, J. Exper. Med. **68**:173, 1938.

Young (12 to 15 day old) mice are approximately as susceptible to the virus of equine encephalomyelitis, Eastern or Western strain, when it is given intraperitoneally as are adult mice when the virus is injected intracerebrally. With this susceptibility to the virus injected by the intraperitoneal route as a basis, intraperitoneal injection of immune serum–virus mixtures was found to result in protection in dilutions which give rise to infection after intracerebral inoculation. The difference in protection by the two indicated routes was shown not to depend on the amount of inoculum or on the age of the mice given intracerebral injections. Incubation at 37 C. for two and one-half hours neither increases nor diminishes the protective action of immune serum when the intraperitoneal method is employed. The phenomenon of selective protection in different tissues is elicited by the serums of hyperimmunized mice, guinea pigs and rabbits and by serums derived from horses infected with the disease in nature or exposed to it by contact with infected animals. Of 4 horses recovered from the malady, all showed antibody in their serum; of 9 others exposed by contact, 4 revealed antiviral bodies when the intraperitoneal technic was employed. These tests on horse serum have pointed to the potential value of this procedure for epidemiologic studies. Finally, the reaction itself has significance through its bearing on the mechanism of immunity.

FROM AUTHORS' SUMMARY.

SMALL COLONY VARIATION IN B. PARATYPHOSIS B (TIDY). A. HADDOW, J. Infect. Dis. **63**:129, 1938.

A description is given of the spontaneous occurrence of dwarf colony variation in a laboratory strain of Bacillus paratyphosus B (Tidy). While the original

variant bore an obvious relation to the normal form of the parent culture, it subsequently yielded a minute colony containing gram-negative coccal forms similar to the G type described by Hadley for Bacterium dysenteriae Shiga and other bacterial species. The biologic characters of this variant are given in detail, and evidence is presented in support of Hadley's contention that such colonies contain filtrable elements. No reversion was obtained, but in the course of propagation over four years the G type gave rise to a number of closely related discontinuous variants, whose features are described. The mode of origin and the nature of the G type in relation to the parent organism are discussed with other cognate topics.

FROM AUTHOR'S SUMMARY.

GROWTH OF PROTEUS. P. FILDES, Brit. J. Exper. Path. **19**:239, 1938.

Nicotinic acid is an essential accessory nutrient for 10 strains of Proteus. It is the only nitrogenous substance required in metabolism which cannot be synthesized from ammonia (NH_3). Its function is to supply material for the synthesis of pyridine nucleotides.

FROM AUTHOR'S SUMMARY.

DARK-GROUND STUDIES OF FLAGELLAR AND SOMATIC AGGLUTINATION OF B. TYPHOSUS. A. PIJPER, J. Path. & Bact. **47**:1, 1938.

An account is given of dark ground methods, with the sun being used as the source of light, by means of which the flagella of Bacillus typhosus and similar bacteria swimming in broth can be seen and photographed. B. typhosus and similar bacteria swim by means of a long tail. At rest, the tail unwinds itself into two rather broadly coiled spiral flagella, which are attached somewhere near the middle of the body of the bacillus and take up a position at an angle to its long axis. When resuming activity, the two flagella start revolving round their own axis, stretch, and become twisted round each other at the rear end of the bacillus, where they form the tail. Each flagellum consists of a number of extremely thin threads, as can be seen when the flagella finally disintegrate. The drying up of a drop of bacterial suspension, such as precedes staining, produces artefacts in the flagellar equipment of bacilli. In so-called H agglutination the actual process is merely a secondary nonspecific mechanical event. The specific phase of H agglutination is that in which the tails and flagella become covered with a granular deposit which finally completely covers and ensheathes them. The resulting thickened and stiff spiral structures cannot escape becoming entangled, and so the bacilli become attached to one another. This is true both for live bacilli and for formaldehydized suspended bacilli. In O agglutination the agglutination is the primary event. Here one can see that the bacilli exert mutual attraction. The force acts in the direction of the long axis of the bacillus which joins with its fellow end to end. This leads to building up of clumps which exhibit a regular pattern. Neither tails nor flagella take part, but their motility and appearance are affected.

FROM AUTHOR'S SUMMARY.

INFECTIOUS ANEMIA OF HORSES. L. BALOZET, Arch. Inst. Pasteur de Tunis **27**: 189, 1938.

The virus of infectious anemia of horses was rendered harmless by treatment with 0.1 per cent sodium ricinoleate. Inoculation of such inactivated virus did not produce immunity in the single donkey treated. Small doses of virus produced only a mild infection in the first donkey inoculated, but in another animal the injection of similar doses resulted in death. Virus mixed with hydrous wool fat and olive oil likewise produced a mild infection in the first animal inoculated and a fatal one in a second animal. Hence attempts to produce an attenuated form of the disease by the use of small doses or by incorporating the virus in a substance tending to prevent its rapid absorption were unsuccessful.

FROM AUTHOR'S SUMMARY.

Immunology

SENSITIZATION WITH HEAT-KILLED TUBERCLE BACILLI. J. FREUND and E. I. OPIE, J. Exper. Med. **68**:273, 1938.

An intracutaneous injection of a small quantity of heat-killed tubercle bacilli into a previously normal animal produces a nodule which persists from eight to twelve weeks; an injection of the same amount into a well sensitized animal produces a lesion which ulcerates within from one to three weeks and is completely healed after about five weeks. Complete healing is functional evidence of the disappearance of the antigen. An intracutaneous injection of heat-killed tubercle bacilli induces more rapid sensitization than a subcutaneous or an intravenous injection, but after repeated injections the difference disappears. An increase in the quantities of heat-killed tubercle bacilli injected or division of the quantity among several simultaneous injections will accelerate sensitization. The rapidity of antibody formation as measured by complement fixation varies in different rabbits under the same conditions, but complement fixation is always demonstrable after repeated injections of heat-killed tubercle bacilli. Antibody formation is more rapid and reaches higher titers with intravenous than with intracutaneous or with subcutaneous injections. It is accelerated by division of the injected antigen among multiple simultaneous injections. Small quantities of BCG induce rapid sensitization and more abundant antibody formation, measured by complement fixation, than the same amounts of heat-killed tubercle bacilli, but with repeated injections the difference disappears. Animals that are sensitized and immunized (allergic) before infection are in most instances more resistant to infection than previously normal animals, but there is no correlation between the intensity of sensitization or the titer of antibodies, on the one hand, and the resistance to infection, on the other. It is probable that the skin test for sensitization and complement fixation as applied to the blood serum measure antibodies or other factors determining sensitization and immunity that are in excess of those actively concerned in the maintenance of resistance.

FROM AUTHORS' SUMMARY.

ANTIGENIC STRUCTURE OF SPERMATOZOA. W. HENLE, G. HENLE and L. A. CHAMBERS, J. Exper. Med. **68**:335, 1938.

By means of the absorption technic as applied to homologous spermatozoal serums, a head-specific and a tail-specific antigen could be demonstrated. Both are heat labile. A heat-stable antigen was found to be common to both the head and the tail. This substance is species specific. Antibodies against the head-specific and the tail-specific antigen led to two different types of agglutination as shown by the slide method. Using heterologous antiserums against spermatozoa, three different cross-reacting antigens could be observed, two in the head and one in the tail. One of the head antigens is not active in the native cell; it comes to action only after breaking of the cell. Antibodies against this substance were not found in antiserums against native bull spermatozoa but were formed when vibrated spermatozoa or heads were injected into rabbits. The cross reactions can be removed from an antiserum leaving the head-specific as well as the tail-specific reaction intact.

FROM AUTHORS' SUMMARY.

INACTIVATION OF TETANUS TOXIN BY CRYSTALLINE VITAMIN C (*l*-ASCORBIC ACID). C. W. JUNGEBLUT, J. Immunol. **33**:203, 1937.

Three preparations of vitamin C (l-ascorbic acid)—a natural crystalline extract, a stable synthetic solution and a crystalline synthetic product—were capable of inactivating 2 minimal lethal doses of tetanus toxin in the test tube but not in vivo within the p_H range of from 6.1 to 6.4 and in quantities varying

from 1 to 10 mg. The inactivation was not due to the chemical reaction, and it differed from the toxin-antitoxin reactions, because it did not follow the laws of multiple proportions.

I. DAVIDSOHN.

EXPERIMENTAL HYPERSENSITIVENESS IN THE RHESUS MONKEY. H. W. STRAUS and A. F. Coca, J. Immunol. **33**:215, 1937.

Induced sensitivity to poison ivy in rhesus monkeys was limited to the isolated portion of the skin of the arm, or to the remainder of the body's surface after an encircling incision of the skin of the arm and dissection downward had interrupted the continuity of the skin. The conclusion is drawn that the sensitivity of contact dermatitis is developed locally in the cells of the epidermis and that the agents that produce hypersensitiveness spread through the oily substances of the skin by continuity and not through the fluids of the body.

I. DAVIDSOHN.

HETEROGENETIC HEMAGGLUTININS IN MAN FOLLOWING THERAPEUTIC INJECTIONS OF IMMUNE SERUM FROM RABBITS. F. SCHIFF, J. Immunol. **33**:305, 1937.

The serums of some patients who had been given injections of antipneumococcus type-specific rabbit immune serums showed rises in agglutinins for the red blood cells of the rabbit, sheep, ox, horse and rhesus monkey. These antibodies behaved much as do the agglutinins that appear following injections of horse serum. The agglutinins for sheep red cells were more readily removed by the red cells of all the species, and, on the other hand, the red cells of the rabbit demonstrated the greatest capacity for absorbing the different hemagglutinins. The antibodies that develop in response to horse and rabbit serum behave differently from those that develop in the serums of patients with infectious mononucleosis. Schiff suggests the term "serum sickness antigen" for the common antigenic substance in the serums of the horse and rabbit and in the red cells of horse, rabbit, sheep and ox. It is heat stable; it has an alcohol-soluble fraction, and it has a water-soluble fraction that can be removed from the alcohol-treated beef cells.

I. DAVIDSOHN.

AGGREGATION OF ANTIBODY-ANTIGEN COMPOUNDS. J. T. DUNCAN, Brit. J. Exper. Path. **19**:328, 1938.

The view that the aggregation of the immune compound is specific in character, as demanded by the lattice hypothesis, is supported by the results of agglutination reactions with immune serum, and, although the effect of a nonspecific factor in aggregation was never absent from the precipitation reactions, its incidence seems to be secondary to a specific combination, and the results of these tests may be accepted as not inconsistent with the lattice hypothesis.

FROM AUTHOR'S SUMMARY.

NATURE OF THE O PROPERTY. L. HIRSZFELD and Z. KOSTUCH, Schweiz. Ztschr. f. allg. Path. u. Bakt. **1**:23, 1938.

In order to ascertain the nature of the agglutinogen in human O blood, Hirszfeld and Kostuch tested members of 58 families with 138 children by means of anti-Shiga bacillus immune goat serum and by means of normal bovine serum—serums both of which had the peculiarity of agglutinating by preference blood belonging to group O. In this study there was one family in which the parents both belonged to subgroup A_1 and a child to subgroup A_2B; this finding was attributed by the writers to illegitimacy. There were no exceptions to the theory of the inheritance of the subgroups of A and AB by four allelomorphic genes, advanced by Thomsen, Friedenreich and Worsaae. The anti-O serums reacted most strongly with bloods belonging to group O, somewhat less intensely with bloods of subgroups A_2 and A_2B, more weakly with bloods of group B and subgroup A_1 and not at all with

bloods of subgroup A_1B. Hirszfeld and Kostuch believe that the ability of bloods of subgroup A_2 to react with anti-O serums is not due to the effect of the O gene in heterozygous blood of this subgroup but indicates that the agglutinogen A_2 represents a less pronounced mutation from agglutinogen O than agglutinogen A_1. Agglutinogen B would hold a place somewhere between A_1 and A_2.

A. S. WIENER.

BLOOD GROUP PROPERTIES IN SHEEP. T. ANDERSEN, Ztschr. f. Rassenphysiol. **10**: 88, 1938.

On the basis of isohemolysis, Andersen was able to confirm the broad classification of sheep blood into three groups, Ro, O anti-R and Oo. When sheep of any group were immunized with blood of other sheep, even those belonging to the same group, immune isohemolysins were readily produced. These immune isoantibodies were qualitatively different from the natural isoantibodies, since they were not absorbable with human A_1 blood. By immunizing rabbits with sheep blood Andersen obtained group-specific hemolysins in about half the rabbits.

A. S. WIENER.

Tumors

CARCINOGENIC ACTION OF METHYL DERIVATIVES OF 1:2-BENZANTHRACENE. M. J. SHEAR, Am. J. Cancer **33**:499, 1938.

Of 21 compounds subcutaneously injected into pure strain mice in tests for carcinogenic activity, 10 produced tumors at the sites of injection. Subcutaneous tumors were produced in mice by 5,10-dimethyl-1,2-benzanthracene about as rapidly as by cholanthrene, showing that the pentacyclic system of the latter is not essential for high carcinogenic potency. The production of subcutaneous tumors by 10-methyl-1,2-benzanthracene with the skin-painting technic was slower than the production of subcutaneous tumors with the injection technic. Tumors were produced by 5,9-dimethyl-1,2-benzanthracene about as rapidly as by cholanthrene. The 9-methyl derivative was also found to be a potent carcinogen, but the latent period was longer than with the 5,9-dimethyl derivative. The 4,10-ace derivative was found to be carcinogenic, especially in small doses which did not produce severe local damage of tissue. The 1′,2′,3′,4′-tetrahydro derivative of 4,10-ace-1,2-benzanthracene was also found to be carcinogenic. 20-ethylcholanthrene produced tumors in a high proportion of the mice but acted more slowly than 20-methyl-cholanthrene or cholanthrene. No tumors were produced by *s*-triphenylbenzene even after twenty months.

FROM AUTHOR'S SUMMARY.

GRANULOSA CELL CARCINOMA. E. H. NORRIS, Am. J. Cancer **33**:538, 1938.

The granulosa cell carcinoma may be defined as a malignant tumor of the ovary the histologic structure of which commonly and characteristically shows the presence of granulosa-like cells which manifest a tendency to surround more or less typical follicles. The tumor is associated with signs and symptoms which may be ascribed to the influence of excessive amounts of estrogen. The granulosa cell carcinoma may develop in any of the decades of life, and the principal clinical manifestations vary with and depend almost entirely on the age of the patient and on the epoch of the female sexual cycle in which the tumor develops. In children the granulosa cell carcinoma is a cause of precocious puberty. In the older age groups the effects are chiefly concerned with menstrual phenomena. The general course of the disease is continuously progressive, and in untreated patients it leads to death from malignant metastases. Early surgical removal of the primary tumor offers the only hope of permanent relief; in general the operative procedure should be of a radical nature. The postoperative result is good, and if the tumor can be removed the symptoms disappear. The differential diagnosis

is not difficult to make on clinical grounds in children or in women past the menopause but may be impossible to make in women seen during the reproductive epoch. The histologic structure of the granulosa cell carcinoma is variable within wide limits; the pattern varies from typical follicle-like structures, broad epithelial bands and narrow cords to carcinoma-like pictures. There seems to be no advantage in a subdivision of granulosa cell carcinoma on the basis of the different histologic patterns.

FROM AUTHOR'S SUMMARY.

HYPOPHYSEAL TUMORS INDUCED BY ESTROGENIC HORMONE. B. ZONDEK, Am. J. Cancer **33**:555, 1938.

Estrogen injected either parenterally or percutaneously into 240 infantile rats caused eunuchoid dwarfing of all of them. Such treatment carried on for four months caused pituitary enlargement in the males; in the females the gland remained grossly normal. After treatment had continued for eight months the pituitaries of 29 of 35 rats, both males and females were transformed into enormous hypophysial tumors. These tumors caused the death of the animals. The duration of treatment was of primary importance, no tumor developing in less than seven months; the size of the dose of estrogen was of only secondary significance. The tumors could be diagnosed by typical clinical symptoms, the most characteristic of which was a decrease in the body temperature. This was shown not to be due to hypoglycemia. The enlarged pituitaries and the tumors contained the same amount of gonadotropic substance as the normal pituitaries of control animals. It was therefore not the production but the utilization of the gonadotropic hormone that was inhibited in the eunuchoid dwarf rats, causing a functional deficiency.

FROM AUTHOR'S SUMMARY.

IMPLANTATION CARCINOMA OF THE TUBAL MUCOSA. J. A. SAMPSON, Am. J. Path. **14**:385, 1938.

The pathogenesis, structure, form and life history of carcinomatous implants of ovarian origin on the tubal mucosa are the same as the pathogenesis, structure, form and life history of similar implants on the peritoneal serosa.

FROM AUTHOR'S SUMMARY.

MORPHOLOGICAL VARIATIONS OF TUMOR CELLS. O. SAPHIR, Am. J. Path. **14**: 443, 1938.

A study of miscellaneous types of carcinoma revealed morphologic variations among the individual tumor cells of particular neoplasms. These morphologic differences were not those always encountered in malignant tumors but were often so heterogeneous as to obscure the exact nature of the tumor. They were principally brought about by the presence of seemingly different types of tumor cells in an individual tumor. Thus, basal cells or transitional cells were found in squamous cell carcinoma. The presence of various types of tumor cells in single tumors may be due to a number of factors, which are discussed. However, the findings presented here seem to indicate that such a tumor arises from an area which a priori contained the various cells of which the tumor consists, or derivatives of these cells. Such morphologic variations must be taken into consideration in the grading of a carcinoma and also in the determination of its sensitivity to radium. The relative resistance to radium shown by basal cell or transitional cell carcinoma in some cases could be ascribed to the presence of many squamous cells in both tumors.

FROM AUTHOR'S SUMMARY.

THE GENETICS OF CANCER IN MICE. J. J. BITTNER, Quart. Rev. Biol. **13**:51, 1938.

From the data tabulated during the past ten years it is evident that some progress has been made in comprehending some of the details of the inheritance of susceptibility to some forms of cancer. Not all types of tumors may be grouped

and studied in a single experiment; each type must be considered by itself. The problem is by no means solved, but a start has been made by the use of homozygous stocks of mice, and geneticists display increasing interest in the problem. Much of the controversy is due to the application of genetic principles to data which are not suitable for this type of interpretation.

Application of the findings in animal experimentation to the disease in man is problematic and remains for the future. The impossibility of securing human data comparable with those on inbred strains of animals whose matings may be controlled needs little comment. The reliability of a considerable proportion of the human data is questionable and leaves much to be desired.

FROM AUTHOR'S SUMMARY.

VISCERAL METASTASIS FROM RECTAL CARCINOMA. C. E. BROWN and S. WARREN, Surg., Gynec. & Obst. **66**:611, 1938.

The tendency of rectal carcinoma to metastasize via the blood stream varies in general with the degree of differentiation. As a rule, the longer the duration of rectal carcinoma the greater is the number of visceral metastases. Metastasis to bone occurred in 5 per cent of the series. The more the primary growth penetrates the wall of the bowel, the greater are the chances of blood-borne extensions. The reliability of a prognosis of visceral metastases based on observation of local intravascular metastasis increases with the duration of the disease. Only 1 of the 70 persons showing visceral metastases failed to show local intravascular involvement, while one fourth of those whose lymph nodes were free from invasion had visceral deposits. Sections of the primary growth in rectal carcinoma should be scrutinized carefully for invasion of capillaries or veins by tumor cells, because such invasion often means visceral metastases, and its absence, provided at least three sections from different parts of the growth have been examined, nearly always rules out visceral involvement. The efficiency of this sign—invasion of capillaries or veins—in predicting visceral or bone metastases outranks that of neoplastic lymph nodes. FROM AUTHORS' SUMMARY (WARREN C. HUNTER).

INFLAMMATION AND CARCINOGENESIS. P. R. PEACOCK and S. BECK, Brit. J. Exper. Path. **19**:315, 1938.

The induction of sarcoma in the connective tissues of mice following injection of 3,4-benzpyrene in various solvents depends more on the rate of absorption of the benzpyrene than on the early local tissue reaction to the solvent. In mice in which benzpyrene is eliminated within three months tumors are rare (5 of 41 surviving for four months); in those in which elimination is delayed beyond six months tumors are common (34 of 46 surviving for four months). Tumors occur at points of optimal concentration of benzpyrene, which in these experiments were found to be a few millimeters away from the principal loci of benzpyrene.

FROM AUTHORS' SUMMARY.

PRECANCEROUS SKIN CHANGES. J. W. ORR, J. Path. & Bact. **46**:495, 1938.

An investigation has been made of the changes in the skin of white mice treated with six carcinogenic hydrocarbons, ten noncarcinogenic hydrocarbons of related chemical structure and a group of unrelated irritants. These substances have been used in solution in benzene and acetone, the latter solvent being of greater value for the present purpose, as it is without effect on normal mouse skin. Early epilation is a striking feature of the action of cholanthrene, methylcholanthrene, 3,4-benzpyrene and 1,2,4,6-dibenzanthracene but not of 1,2,5,6-dibenzacridine and 3,4-benzphenanthrene. It occurs with some noncarcinogenic hydrocarbons but to a much less extent than with the four most potent carcinogens. After epilation by a carcinogen, the regenerated hair is abnormal. The appearance of tumors is preceded by progressive thickening and loss of elasticity and

by passive congestion of the skin. Ulceration of the surface does not bear any relationship to tumor formation. Histologically, the carcinogens produce squamous hyperplasia of the epidermis in the first weeks of treatment. Thereafter, the progressive changes are found in the deeper tissues, and the most significant phenomena are: (1) transformation of the collagen of the superficial, and later of the whole, dermis into a fine-fibered, nonrefractile type; (2) passive congestion of the subcutis; (3) alterations in the texture of the elastic tissue without necessarily an increase in its amount, and (4) absence of inflammatory cell infiltration. When tumors appear, they are frequently related to fibrous scars in the subcutis, to the gaps in the elastic tissue of the dermis or to both. In comparing the carcinogens it was observed that the rate of progress of the changes cited corresponds with the rapidity with which tumors are induced. Similarly, mice in which tumors appear early or late are those in which these changes advance rapidly or slowly, respectively. When comparable changes occur with noncarcinogenic applications, evidence of inflammation is usually present. It is suggested that the cancerization of the epithelial cells by the carcinogenic hydrocarbons is at any rate partly the result of the changes in the deeper tissues and that its mechanism may be related to the consequent interference with their nutrition.

FROM AUTHOR'S SUMMARY.

MESOTHELIOMA OF THE PLEURA. L. CORNIL, V. AUDIBERT, L. MONTEL and M. MOSINGER, Bull. Assoc. franç. p. l'étude du cancer **27**:51, 1938.

The article contains a comprehensive 40 page review of the subject of primary tumors of the pleura. Two cases, one of primary mesothelioma, the other of secondary carcinoma, are reported. The secondary tumor presented diagnostic difficulties, as the primary tumor could not be found. The squamous cell structure of the growth, which covered the entire pleura, suggested that the primary tumor was in the periphery of the lung. The other tumor occurred in a 31 year old man with a serofibrinous and later a hemorrhagic pleural effusion, with fever and with loss of weight of eight months' duration. Twenty-one months after the onset a nodule developed in the wall of the chest. It had the structure of a sarcoma. At necropsy the whole lung was encased in a shell from 25 to 30 mm. thick. Many small cysts filled with a hemorrhagic fluid and many nodules, ranging in size to that of a fist, were seen. The pulmonary parenchyma was not involved. Histologic sections showed a great variety: accumulations of epithelial-like cells, tubular structures lined with low cuboidal cells, some areas resembling mixed tumors of the salivary glands, others of a fibrous, of a fibrosarcomatous and of an angiomatous character, and accumulations of tumor giant cells. A detailed analysis of the varied histologic features of the reported cases is given, as well as a discussion of the hypotheses dealing with the histogenesis of the pleural lining. The histologic polymorphism of most primary tumors of the pleura is in accord with Maximow's concept of the multiple potentialities of the pleural mesothelium.

I. DAVIDSOHN.

GANGLION CELL TUMORS OF THE BRAIN. E. CHRISTENSEN, Virchows Arch. f. path. Anat. **300**:567, 1937.

Thirty-seven tumors of the brain containing ganglion cells are tabulated and briefly reviewed. The varying nomenclature of these tumors, depending on the degree of differentiation, is discussed. The author describes 5 of the tumors. Four revealed a considerable degree of differentiation and were considered histologically benign. The fifth was believed to have arisen on the basis of congenital dysplasia. Most of the tumors arose in children and young adults. In 30 per cent of the series the growth occurred in the floor of the third ventricle. Because of the histologically benign character of many of these tumors the postoperative prognosis should be good if such a tumor is so situated that it can be completely removed.

O. T. SCHULTZ.

HISTOGENESIS OF THE SHOPE INOCULABLE RABBIT PAPILLOMA. P. LADEWIG and S. OBERNDORFER, Virchows Arch. f. path. Anat. **301**:204, 1938.

The histogenesis of the inoculable rabbit papilloma described by Shope in 1933 was studied in inoculated areas of skin removed at intervals of from one to three hundred and thirty-four days after inoculation. On the fifth day there begin to appear within the epidermis small areas, termed primary centers, each composed of a small number of swollen, faintly stained epithelial cells. These cells are not capable of division. Such centers continue to increase in number from the sixth to the ninth day, and during this period proliferation of the malpighian layer becomes evident. In time the barrier between epithelium and connective tissue is broken down, and a "precancerous" stage develops. The various types of epithelial cells composing the papilloma are derived from similar cells of the normal epidermis. The various cell inclusions observed are not characteristic of the rabbit papilloma but are seen in dyskeratotic lesions of the human skin. They are derived from substances formed within the epithelial cells. Elementary virus bodies have not been seen.

O. T. SCHULTZ.

THE NEVUS CELL. F. FEYRTER, Virchows Arch. f. path. Anat. **301**:417, 1938.

Although Soldan described the origin of cellular nevi from the terminal nerves of the skin in 1899, the neurogenic origin of nevi did not receive much attention until the much more recent work of Masson. Soldan derived the nevi from the connective tissue of the terminal nerves, whereas Masson derived them from the cells composing the sheath of Schwann and considered the nevus cell a special type of cell. Feyrter presents a monographic study of the nevus cell, based largely on the use of a metachromatic toluidine blue–staining method, which he has previously described. The nevus cells contain lipoid substances of various kinds in the form of fine droplets, large vacuoles or crystals. At the periphery of the cell the material may become fibrillated, the fibrils becoming continuous as precollagen with the intercellular fibrils. Lamination of the cells leads to the formation of bodies like the Meissner tactile corpuscles described by Masson. Feyrter claims to have demonstrated lipoid-containing cells in the epidermis (the intraepidermal pale nevus cells of Masson), at the junction of the epidermis with the cutis and in the cutis in the absence of nevus. It is their function to elaborate, store and utilize lipoids. They are part of a system which in the nerve fibers is the endoneurium and in the skin may give rise to the isolated cells described. These cells of the endoneurium Feyrter terms endothelium, and it is from them that the nevus cell is derived. The nevus, therefore, is a neurogenic endothelioma or neurendothelioma.

O. T. SCHULTZ.

Medicolegal Pathology

CHEMICAL TEST OF THE BREATH FOR INTOXICATION. R. N. HARGER, E. B. LAMB and H. R. HULPIEU, J. A. M. A. **110**:779, 1938.

A reagent for alcohol in the breath consists of 55 per cent sulfuric acid containing a measured small amount of permanganate solution. The permanganate reacts rapidly and quantitatively with alcohol at ordinary temperatures and is not affected by acetone.

The ratio of alcohol to carbon dioxide in the breath may be used to measure the concentration of alcohol in the blood. The weight of the alcohol accompanying 190 mg. of carbon dioxide in the breath is very nearly equal to the weight of the alcohol in 1 cc. of the subject's blood.

Employment of the ratio of alcohol to carbon dioxide in the breath permits the test to be made without the subject's being touched. A tube is held in the breath stream, and a pump draws the sample through the apparatus.

Tests made on 121 subjects showed a good correlation between the concentration of alcohol in 1 cc. of the blood and the amount of alcohol accompanying 190 mg. of carbon dioxide in the breath.

As collected in our tests, 4 liters of expired air contained about the same amount of alcohol as 1 cc. of the subject's blood. Because of possible fluctuations in the amount of alveolar air in such samples, it is believed that analyses of breath made on the volume basis should be checked by determining the carbon dioxide in the sample.

FROM AUTHORS' SUMMARY.

MEDICOLEGAL SIGNIFICANCE OF PRESSURE ON THE BRAIN. W. NEUGEBAUER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **29**:272, 1938.

Pressure on the brain is an expression of imbalance between the intracranial space and its solid and liquid elements. The pressure may be acute or chronic, latent or manifest. Usually the brain with its enveloping membranes is from 10 to 14 per cent smaller than the cranial cavity. Acute pressure is divided into two types: that due to edema of the brain and that due to swelling of the brain. The latter is difficult to recognize in children, but the brain is definitely more dense than when the pressure is due to edema. Acute pressure is brought about by trauma, including birth trauma, and by subdural and epidural hemorrhage. It may occur after the action of toxins; thus it is found after burns, in gastrointestinal catarrh in children, in rickets, and in uremic and diabetic coma. Exogenous toxins, such as alcohol, ether and chloroform, and poisons, such as lysol (compound solution of cresol), may also cause it. It is frequently seen in infections such as cerebrospinal meningitis.

Chronic pressure is manifest in alterations of the skull, among which are deep furrows for the arteries and thinning of the sella turcica. The dura often is thickened and has coarse pacchionian granulations. The leptomeninges may be edematous and at times calcified. Prolonged pressure may cause synostosis of the sutures. The chronic alterations associated with tumors are well known.

GEORGE J. RUKSTINAT.

INJURIES OF THE CERVICAL SPINAL CORD IN NEWBORN CHILDREN. F. HAUSBRANDT, Deutsche Ztschr. f. d. ges. gerichtl. Med. **29**:353, 1938.

Hausbrandt believes that at times minor alterations in the cervical portion of the spinal cord are regarded by pathologists as a cause of death, although, practically, they have no significance. Not every tear of the tentorium leads to death, as such tears have been encountered in children who survived such tears up to twenty days and then died of intercurrent infections. This is especially true of premature infants. When, on the other hand, the physiologic tension of the tentorium is altered because of the site of tears in it, pressure on the head in the birth canal is applied to the medulla oblongata so that the stimulus to respiration is initiated. The same pressure effects may be at work where there is massive hemorrhage in the posterior cranial fossa. The term "aspiration of amniotic fluid" does not indicate either a definite process or a clearcut diagnosis.

After a detailed technical consideration of the method to be employed in removing the spinal cord, the author discusses the pathologic changes he has encountered. Hemorrhage was found in the epidural space of the cervical region in some of the bodies examined, but it was not a regular accompaniment of intracranial hemorrhage. Usually such hemorrhages were associated with extensive injuries of the cervical part of the spinal cord; they occupied the upper portion and showed gradation from a bloody edema to massive, sleevelike hemorrhages. Subdural hemorrhages were less frequent and extensive than epidural ones and usually were continuations of infratentorial extravasations. Hemorrhages in the meninges were relatively rare. Injury of the cord near its junction with the medulla was seen very frequently in full term stillborn children and in those dying shortly after birth. Regions of softening and hemorrhage were found most often at the junction of gray and white matter. The white substance was usually spared, but isolated or clumped hemorrhages were common in the region of the posterior horn.

GEORGE J. RUKSTINAT.

Society Transactions

NEW ENGLAND PATHOLOGICAL SOCIETY

CHARLES BRANCH, *President*

Regular Meeting, Feb. 16, 1939

GRANVILLE A. BENNETT, *Secretary*

CORRELATIONS BETWEEN POSTMORTEM TELEROENTGENOGRAMS OF THE CHEST AND AUTOPSY REPORTS, WITH SPECIAL REFERENCE TO PULMONARY EMBOLISM AND INFARCTION. BENJAMIN CASTLEMAN and (by invitation) AUBREY O. HAMPTON.

Accurate correlations between roentgenographic and autopsy observations are usually impossible because of the pathologic changes that frequently occur between the taking of good roentgenograms and death, the unsatisfactory quality of antemortem roentgenograms on films which of necessity are often portable and because of the collapsed state of the lungs post mortem.

In order to avoid these difficulties we are now taking anteroposterior and lateral postmortem roentgenograms of the chest at a distance of 7 feet (2 meters), with the subject upright. At autopsy the lungs, instead of being sectioned in their fresh state, are distended to approximately their inspiratory size by pouring solution of formaldehyde U. S. P. into the trachea. The trachea is then tied and the entire preparation put in solution of formaldehyde. One week later the the lungs are sectioned in the presence of the roentgenologist, and an attempt is made to account for every shadow on the roentgenograms. Lungs from 400 persons have been examined in this way.

In 3,500 routine autopsies, 9 per cent showed embolism or infarction of the lung, and in 3.5 per cent embolism was the cause of death. In this series of 400 autopsies 14 per cent showed embolism or infarction—an increase of 50 per cent. Molds were made of many of the infarcts, and none showed the traditional triangular shape. Frequently an infarct in the costophrenic angle showed a convexity toward the hilus. Every infarct observed was peripheral, extending to the pleural surface of the lung. More frequently infarction occurred in areas where two or more pleural surfaces met.

From this study we have been able to obtain a fairly clear picture of the successive pulmonary changes that develop when an embolus reaches the lung. During the first day the infarcted lung still contains a good deal of air in the alveoli, and there is no sharp line of demarcation between infarcted and normal lung, nor is there any destruction of alveolar walls. Some air-containing alveoli are still present on the third day, but at this time a sharp line of demarcation is present, and red blood cells and white blood cells are found in the pulmonary alveoli and in their walls. Still later, the infarcted areas become encapsulated, and there is almost complete necrosis of the alveolar walls. Complete healing is evidenced by an organized fibrous scar, which shows as a linear shadow on the roentgenogram. Pathologists have been too lax in searching for or recognizing these healed infarcts, probably because the infarcts are difficult to find when the lungs are deflated.

One of the most important aspects of this work is the development of the concept of incomplete infarction. The term "incomplete infarction" is used to indicate an infarct in which the alveoli are partially filled with air, edema fluid, red cells and a few leukocytes but in which there is no destruction of the alveolar wall. These lesions do not organize like true infarcts but resolve in a few days.

They are seen most commonly in postpartum or postoperative patients. Temporarily, however, the roentgenologic and even the gross postmortem appearances may be indistinguishable from true early infarction. This condition occurs in a previously normal lung (if it took place in a congested lung, a true infarct would develop) and corresponds to the experimental lesions produced in normal dogs by such workers as Cohnheim, Litten and Karsner. These investigators considered such lesions as negative results, since there was no destruction of the alveolar wall. Clinical application of these negative results has not been made previously.

CHRONIC BENZENE POISONING. FRANCIS T. HUNTER (by invitation).

The report concerns clinical and hematologic studies made on 80 workers exposed to fumes of benzene, including 8 with clinical poisoning. Only 30 per cent of the 80 workers were thought to show no effects of the solvent. In the whole group, however, polycythemia occurred in 17.5 per cent and anemia in 29 per cent. In 12 workers (15 per cent) unexplained leukocytosis was present without other changes in the blood. A single patient had leukopenia without other changes.

The descending order of frequency of variations from the normal peripheral blood picture was leukocytosis, 34 per cent; decrease in the percentage of polymorphonuclears, 31 per cent; anemia, 29 per cent; presence of young polymorphonuclears with or without marrow cells, 28 per cent; absolute decrease in the number of polymorphonuclears, 26 per cent; eosinophilia, 25 per cent; polycythemia, 17.5 per cent; absolute increase in the number of polymorphonuclears, 17.5 per cent; leukopenia, 15 per cent; increased percentage of polymorphonuclears 5 per cent.

It is concluded that leukopenia is a poor index as to the effect of benzene on the marrow. In 10 of 12 instances in this series, when leukopenia was noted anemia was already present. Leukocytosis, a decreased percentage of polymorphonuclears, the presence of young polymorphonuclears or marrow cells, or eosinophilia is observable prior to the establishment of anemia. In some cases polycythemia may be the earliest detectable finding.

In 3 fatal cases the symptoms of poisoning appeared months after removal from exposure and seemed to be precipitated by the onset of an otherwise benign infection. This suggests that the mildly poisoned marrow may be adequate for normal demands but becomes decompensated under the added burden of infection.

HISTOLOGIC STUDIES OF CHRONIC BENZENE POISONING. E. A. GALL and TRACY B. MALLORY.

Histologic material from 14 persons with chronic benzene poisoning has been studied. Twelve of these persons were given complete autopsies, and 2, sternal biopsies.

The literature conveys the impression that benzene characteristically produces aplasia of the bone marrow, and when any attention has been directed to the extramedullary viscera the comments have implied that changes in these organs are unusual and adventitious.

Of the 12 persons examined post mortem, all showed evidence of primary benzene effects on the bone marrow, spleen, liver and lymph nodes. Bone marrow was hypoplastic in only 5, and in none was there total aplasia. Early changes consisted in marked increase of phagocytic activity, hemosiderosis and progressive fibrosis. Following a transitory increase in marrow fat, hemopoietic regeneration, almost wholly erythrogenic, developed. At first the regenerated cells were predominantly normoblasts, but later large numbers of "megaloblasts" and megakarocyte-like cells appeared. These were associated with numerous mitotic figures.

The splenic and lymph node response likewise showed increased phagocytic activity and progressive fibrosis. Lymphoid elements were at first diminished, but they rapidly regenerated. Such regeneration was bizarre, however, and was

accompanied occasionally in the lymph nodes and frequently in the spleen by well defined hemopoiesis. With increasing chronicity there eventually appeared primitive red cells and multinucleated giant cells in such enormous numbers as to obscure the normal architecture.

Changes in the liver consisted only in marked phagocytic activity and relatively minimal megaloblastic and megakarocytic hemopoiesis.

The intense cellularity noted in late stages of this process as observed in bone marrow, spleen and lymph nodes, associated with rapidity of growth, immaturity of component cells, fibrosis and multinucleated giant cells simulating megakarocytes, produced a superficial similarity to Hodgkin's sarcoma. No evidence of metastatic propensity or of involvement of organs not related to the reticuloendothelial system was, however, observed.

Book Reviews

Animal Pathology. Russell A. Runnells, D.V.M., M.S., Associate Professor of Veterinary Pathology, Iowa State College. Price, $6. Pp. 464, with 127 illustrations. Ames, Iowa: Collegiate Press, Inc., 1938.

This is a textbook for elementary courses in pathology given in veterinary schools, usually in the second year of the curriculum. It is intended to serve as an introduction to the study of clinical veterinary medicine. Consequently it deals with animal pathology in its relations to current veterinary practice. It does not aim at comprehensive consideration of animal pathology in general. It is divided into three parts. The first part gives in condensed form a good summary of general pathology, that is "the general pathologic conditions which may occur in more than one tissue or organ." The second part deals with systemic pathology and the third with the special pathology of the various infectious diseases. These two parts are the author's book "A Guide to the Study of Special Veterinary Pathology" in revised and enlarged form. The illustrations are almost without exception instructive if not always artistic; many are taken from the *Journal of the American Veterinary Medical Association.* At the end of each chapter is a short list of appropriate references. The book will serve usefully as an introductory guide to the study of veterinary medicine.

Surgical Pathology. William Boyd, M.D., LL.D., M.R.C.P. (Edinburgh), F.R.C.P. (London), Dipl. Psych., F.R.C.S., Professor or Pathology, University of Toronto. Fourth edition, revised. Price, $10. Pp. 886, with 491 illustrations. Philadelphia and London: W. B. Saunders Company, 1938.

Inguinal lymphogranuloma, grading of carcinoma, glomangioma, parathyroid tumor, autolytic peritonitis, arrhenoblastoma, certain ovarian tumors, regional ileitis and other new topics receive brief consideration, but nothing is said about the "surgical pathology" of the larynx, lungs, pericardium and heart. Certainly the advances and activities in the field of thoracic surgery should be reflected in a book on "surgical pathology." New material has been introduced in the chapters on cancer, thrombosis, gastric ulcer, puerperal sepsis and appendicitis. The chapter on the surgeon and the laboratory is long out of date.

Études sur la rage. P. Remlinger, directeur de l'Institut Pasteur de Tanger, and J. Bailly, chef de service a l'Institut Pasteur de Tanger. Price, 40 francs. Pp. 174. Paris: Masson & Cie, 1938.

P. Remlinger was director of the Institut antirabique de Constantinople from 1903 to 1910. In an appendix are listed the papers published by him on rabies during that period. Several years later he became director of the Pasteur Institute of Tangiers, Morocco, S. Africa, and from 1917 to 1937, inclusive, he published as a single or as a joint author 201 papers on the results of scientific studies of rabies. The papers are listed in chronologic order. The book gives concise summaries of these contributions from the Tangiers period, which concern many various phases of rabies in man and animals. The book will interest especially the scientific student of rabies.

Books Received

TROPANOL ET PSEUDOTROPANOL. ACTIONS PHYSIOLOGIQUES COMPARÉES. René Hazard, Professeur à la Faculté de Médecine de Paris. Paper. Pp. 88, with 24 illustrations. Price 25 francs. Paris: Masson & Cie, 1939.

LA MORT DES BRULÉS. ETUDE EXPÉRIMENTALE. Louis Christophe, Chargé de cours à l'Université de Liége. Preface by Professeur Léon Binet. Paper. Pp. 84, with 19 illustrations. Price, 40 francs. Paris: Masson & Cie, 1939.

CLINIQUE ET PATHOLOGIE COMPARÉES: VÉNÉRÉOLOGIE, CANCÉROLOGIE, DERMATOSES, MÉDECINE GÉNÉRALE, PHYTOPATHOLOGIE. Louis Bory, Chef de clinique a l'Hôpital Saint-Louis. Preface by Professeur M. Fiessinger. Paper. Pp. 240. Price 50 francs. Paris: Masson & Cie, 1939.

THE FIFTY-FOURTH ANNUAL MEDICAL REPORT OF THE TRUDEAU SANATORIUM AND THE THIRTY-FOURTH MEDICAL SUPPLEMENT FOR THE YEAR ENDING SEPTEMBER 30, 1938, TOGETHER WITH THE TWENTY-SECOND COLLECTION OF THE STUDIES OF THE EDWARD L. TRUDEAU FOUNDATION FOR RESEARCH AND TEACHING IN TUBERCULOSIS, 1938.

THE SARANAC LABORATORY FOR THE STUDY OF TUBERCULOSIS OF THE EDWARD L. TRUDEAU FOUNDATION: REPORT OF THE DIRECTOR AND FINANCIAL REPORT FOR THE YEAR ENDING SEPTEMBER 30, 1938. REPRINTS OF SCIENTIFIC PAPERS. Saranac Lake, N. Y.: The Saranac Lake Academy of Medicine, 1938.

INTRACRANIAL TUMORS OF INFANCY AND CHILDHOOD. Percival Bailey, Douglas N. Buchanan and Paul C. Bucy, University of Chicago Clinics. Cloth. Pp. 598, with 113 illustrations. Price $5. Chicago: University of Chicago Press, 1939.

CLASSIFIED AND ANNOTATED BIBLIOGRAPHY OF SIR WILLIAM OSLER'S PUBLICATIONS (BASED ON THE CHRONOLOGICAL BIBLIOGRAPHY OF MINNIE WRIGHT BLOGG). Edited by Maude E. Abbott, B.A., M.D., L.L.D. (McGill). Second edition, revised and indexed. Pp. 163. Price $2.25. Montreal: 1939.

Reprinted with additions from the Sir William Osler Memorial Volume of the International Association of Medical Museums (Bulletin IX, 1926, pp. 437-605).

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VOLUME 27 NUMBER 6

ARCHIVES OF PATHOLOGY

JUNE 1939

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second Class Matter Jan. 30, 1926, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

THE ARCHIVES OF PATHOLOGY is published by the American Medical Association as a medium to advance pathology in the United States and to promote research and observation in this field.

Manuscripts for publication, books for review and correspondence relating to contributions should be sent to Dr. Ludvig Hektoen, Chief Editor, 630 South Wood Street, Chicago, or to any other member of the Editorial Board. Communications regarding subscriptions, reprints, etc., should be addressed, ARCHIVES OF PATHOLOGY, American Medical Association, 535 North Dearborn Street, Chicago.

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The ARCHIVES OF PATHOLOGY is published monthly. The annual subscription price (for two volumes) is as follows: domestic, $6.00; Canadian, $6.40; foreign, $7.00, including postage. Single copies, except the July 1938 issue, are 75 cents, postpaid; the July issue, $2.00.

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